PHOTO QUIZ: An unusual cause of rectal bleeding, see page 407

Mediastinal emphysema complicating diabetic ketoacidosis
- Liver transplantation
- Intracranial multiple midline germinomas
- Reversible hypogammaglobulinaemia
- Disseminated intravascular coagulation and a negative D-dimer test

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Ageing and polymorbidity: is there a mismatch between the training of internists and the need?

A.C. Nieuwenhuijzen Kruseman*, W.J. Mulder, E. Pijpers

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The Dutch population is ageing, like the populations of the majority of countries throughout the world. At present about 15% of the Dutch population is older than 65 years. This will be 21% in 2025. As chronic diseases often develop in elderly people, the Dutch National Institute for Public Health and the Environment (RIVM) recently calculated the consequences of ageing for the Dutch population.1 Calculations were carried out with a ‘Chronic Disease Model’, simulating the course of diseases in the general population, including trends in the past, unhealthy lifestyles and demographic changes due to ageing. The outcome of these calculations is dramatic. About 6% of the Dutch population and about 25% of the people older than 65 years will suffer from diabetes in 2025, if the present trend in the increase of obesity continues. Relative to 2005, this means an increase of 70% in 20 years. Expected prevalences for other chronic diseases are summarised in table 1. In addition, the prevalence of a variety of other chronic diseases related to ageing, such as dementia, depression, anxiety, Parkinson’s disease and hearing and vision impairment, are expected to increase as well. This is not a national trend. At present, chronic diseases contribute 60% to the global burden of disease and this will increase to 80% by the year 2020.6

So, chronic diseases are becoming a major problem in the provision of medical care. As single occurrence of chronic diseases in elderly people is rare, an increasing number of individuals with a chronic disease will suffer from more than one chronic condition.3,5 This requires an integrated patient-centred rather than disease-centred approach, preferably by a generalist. The majority of chronic diseases of these polymorbid elderly patients fall within one or more of the subspecialities of internal medicine and hence internists will become more and more involved in the care of patients with complex multiple conditions. For this reason, the Dutch Society for Internal Medicine recognised internal medicine for elderly patients as a subspecialty in 2004. One may wonder, however, whether or not this is a pleonasm in view of the ageing of the population and passes over what the core competence of a future internist should be: a generalist with knowledge of ageing and the pathophysiology of age-related diseases, an open mind for psychosocial aspects in the care of the elderly and its consequences for a functional and multidisciplinary approach in the provision of care. In view of this, one may also wonder whether there is a need for a specialisation in geriatric medicine separate from internal medicine rather than integration of this speciality within the core competence of general internists to limit fragmentation of care for the elderly patient.

The consequence of this line of reasoning is that the need for internists trained in general rather than subspeciality internal medicine should increase during the next 20 years in parallel with the increase in elderly patients with multiple chronic conditions. The trend in the training of Dutch internists is, however, exactly the opposite. A recent survey revealed that over 90% of the trainees in internal medicine prefer training in one of the subspecialties of internal medicine.6 Of these, trainees’ interest in a training in the subspeciality elderly or geriatric medicine is about 3%, which in combination with the slight interest to become a generalist is not nearly enough to cover the future needs in the medical care of complex polymorbid patients.

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**Table 1. Increase of prevalence (%) of chronic diseases in period 2005-2025**

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer:</td>
<td></td>
</tr>
<tr>
<td>• Lung cancer</td>
<td>47</td>
</tr>
<tr>
<td>• Breast cancer</td>
<td>30</td>
</tr>
<tr>
<td>• Colon cancer</td>
<td>45</td>
</tr>
<tr>
<td>Cardiovascular disease:</td>
<td></td>
</tr>
<tr>
<td>• Acute myocardial infarction</td>
<td>38</td>
</tr>
<tr>
<td>• Heart failure</td>
<td>34</td>
</tr>
<tr>
<td>• Stroke</td>
<td>37</td>
</tr>
<tr>
<td>Chronic obstructive lung disease</td>
<td>19</td>
</tr>
<tr>
<td>Diabetes mellitus:</td>
<td></td>
</tr>
<tr>
<td>• Basic trend</td>
<td>58</td>
</tr>
<tr>
<td>• Including increase of obesity</td>
<td>71</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>41</td>
</tr>
</tbody>
</table>
situation is not unique either. A survey among internal medicine residents-in-training in the USA revealed a steady decline in the percentage of residents planning to pursue generalist careers. In 2003, 20% of the third-year residents planned to practise general internal medicine compared with 54% in 1998. The same trend is noticed in many European countries and has raised growing concerns about the position and future of internal medicine.

Is internal medicine indeed facing a serious problem if this mismatch between medical care needs and career planning continues? We feel it is, and this will have significant consequences for the medical care of the increasing number of elderly patients with complex and multiple chronic diseases. These consequences are diverse. Medical care for polymorbid patients provided by subspecialists rather than generalists will be in danger of becoming more and more fragmented rather than integrated due involvement of multiple specialities – even multiple internists – who act independently, working from the perspective of their own subspecialty and performing either more or less diagnostics and therapeutic procedures than necessary. This may contribute to more visits to the hospital or more hospital-days and accordingly more burden of disease and medical expenses than necessary.

In a recent study on elderly patients with diabetes mellitus managed by a specialist clinic for diabetes care we found a variety of complicating and concurrent morbidities in all subjects necessitating involvement of on average five (sub)specialists and 12 hospital visits per year. Another study on subjects with diabetes showed that both diabetes-related and nondiabetes-related comorbidities increase the use of medical care facilities substantially, in particular for patients with both types of comorbidities. A study on patients admitted because of community-acquired pneumonia, acute myocardial infarction, congestive heart failure or upper gastrointestinal haemorrhage showed longer lengths of hospital stays and slightly higher mortality rates for patients cared for by subspecialists practising outside their specialty, compared with general internists and subspecialists practising within their specialty. These observations are particularly relevant for elderly patients with polymorbid conditions and emphasise that a patient-centred rather than disease-centred approach of integrated care is necessary to meet the complex medical care demands of such patients.

The question that then remains is: ‘Why do trainees in internal medicine prefer a career in a subspeciality instead of general internal medicine?’ With respect to content, it appears that trainees feel that the knowledge and skills they are expected to master for the broad field of general internal medicine exceeds the limits of their capacities. In addition, expertise in one of the subspecialities of internal medicine is considered more prestigious than general expertise and is thought to improve the chances of getting a position in one of the nonuniversity hospitals after the vocational training. This can, however, be questioned as in the majority of advertisements for internist positions, expertise in general internal medicine in combination with preferably more than one subspeciality is emphasised. On the other hand, studies in the USA indicate that the choice for a career as generalist is influenced by opportunities for long-term relationships with patients, a broad content area of practice, caring for ambulatory patients, and time with family. Whether or not this also applies to the Dutch situation is unknown.

What needs to be done to increase the number of trainees pursuing a career in general internal medicine in line with the future needs? To this end, the European Federation for Internal Medicine (EFIM) proposed a number of recommendations in its recent position paper. Among other things, these include the advice to check and adapt the specialist training programmes to the challenges of the profession, to promote a situation in which departments of internal medicine cooperate rather than compete with their subspeciality disciplines, to promote recognition of internal medicine as a discipline in itself rather than a little of this or that, and to improve the marketing of internal medicine to make known to decision-makers, the general population and the patient what internal medicine can offer the health care system and in particular the individual patient with complex polymorbid conditions. We feel, however, that these recommendations will get stuck in the mire of good intentions if they are not translated into practical policies. First, on the basis of the medical care needs, an inventory should be made of how many general and subspecialist internists are needed. The training capacity should be adapted to these needs. In other words, more training positions for generalists and less training positions for subspecialists. An alternative to this can be the introduction of a variety of profiles within the training programmes of internists at the cost of subspeciality training programmes. Or, as in the United Kingdom, to stimulate subspecialists to register also in geriatric medicine to enable them to provide both general and organ specific services. Second, stakeholders in internal medicine should play a key role in the promotion of general internal medicine, not only as a necessity but also as an attractive career choice. Third, administrators and internal medicine partnerships in nonuniversity hospitals should be stimulated to give priority to the recruitment of specialists who consider an integrated approach in internal medicine to be a core competency. Finally, the reasons why trainees turn away from general internal medicine should be analysed to develop specific measures for achieving enough trainees who consider the care of complex and multiple chronic diseases in elderly patients a challenge and not a second choice if they cannot obtain a training position in a subspecialty.
REFERENCES

The diagnosis of disseminated intravascular coagulation made easy

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Disseminated intravascular coagulation (DIC) is a complication of many disorders that are associated with a systemic inflammatory response and is increasingly appreciated as a pathogenetic pathway contributing to organ dysfunction, for example in sepsis, severe trauma or other conditions. Any form of systemic inflammation will virtually always be associated with activation of coagulation, ranging from changes in molecular markers in coagulation factors with equivocal clinical significance to its most full-blown variant, known as disseminated intravascular coagulation (DIC). Until recently, a diagnosis of DIC in routine clinical practice was hampered by the limited availability of reliable and simple tools with sufficient diagnostic accuracy. Indeed, no single clinical or laboratory test has an adequate sensitivity and specificity to confirm or reject a diagnosis of DIC. However, combinations of several readily available coagulation tests may be helpful to establish this diagnosis. Following a previously developed Japanese scheme, the subcommittee on DIC of the International Society of Haemostasis and Thrombosis has proposed a simple scoring algorithm using the platelet count, a prolongation of the prothrombin time, a decreased fibrinogen, and plasma levels of a fibrin-related marker, such as D-dimer or other fibrin degradation products. Importantly, the score can only be used if the patient has been diagnosed with an underlying condition known to be associated with DIC. The various components of the scoring algorithm are assigned points and based on retrospective data a score of ≥5 is compatible with DIC. Prospective validation of this system in consecutive patients with a clinical suspicion of DIC confirmed a high sensitivity and specificity of this scoring system. Moreover, application of the score in large databases of patients with severe sepsis has revealed that the DIC score is a strong and independent predictor of mortality and that the scoring system may select patients who will have a relatively large benefit from interventions in the coagulation/inflammatory cascades, such as the administration of recombinant human activated protein C. Based on these observations, the DIC scoring system may be a helpful tool in clinical practice but also in the design and execution of trials aimed at improving the clinical management of patients with DIC and associated conditions.

However, although the diagnosis of DIC is greatly facilitated by this scoring algorithm, some problems remain. One of these problems is well illustrated by the case report by Constantineacu et al. in this issue of the Netherlands Journal of Medicine. The scoring system uses a ‘fibrin-related marker’, which in most institutions will be an assay for fibrin degradation products. Many routine laboratories are now employing D-dimer assays around the clock to enable the exclusion of venous thromboembolism (VTE) in low-risk patients and indeed the D-dimer assay has been found serviceable for the DIC score. However, we need to realise that there are a large number of different D-dimer assays, each with different sensitivities and specificities for various conditions. In fact, the case by Constantinescu et al. clearly illustrates that the initially used D-dimer assay apparently had a much lower sensitivity for the diagnosis of DIC than the alternative, more commonly used assay. We need to learn from this observation that each different D-dimer assay needs to be validated before it can be used for a specific clinical question, such as the exclusion of VTE or the diagnosis of DIC. The optimal cut-off for the D-dimer assay in the DIC score needs to be determined as well. A previous study showed that for each different D-dimer assay optimal cut-off points for the DIC score can be defined. Most prospective studies on the international DIC score now use values above the upper limit of normal of a given D-dimer test as a ‘moderately increased’ test result, whereas a value that is five times higher than the upper limit of normal would qualify for a ‘strongly increased’ test result. Another difficulty of the current international system may be its static nature, thereby not taking into account dynamic
changes in the respective parameters over a certain period of time. In fact, in the report by Constantinescu et al. the patient had a normal, albeit relatively low, platelet count. However, if we assume that the pre-existent platelet count in this patient with extensive malignancy was $400 \times 10^9$/l, it would mean that more than one trillion platelets would have been consumed in a short time span as a result of coagulation activation. Hence, more dynamic measurements may yield a more sensitive measure of ongoing activation of coagulation. In fact, previous reports on a simplified DIC score, solely based on evolvement of the platelet count and the prothrombin time over time, confirm this notion. A prospective exploration of this system in patients with severe sepsis showed a good correlation with organ failure and provided useful information as to the evolvement of the clinical condition of the patient. These observations are in line with a recent report, demonstrating that a composite dynamic coagulopathy score was quite accurate in identifying patients who would progress to multiple organ failure and who would not survive. Taking these two reports together, it seems that adding dynamic changes to scoring systems for DIC may result in valuable improvement in the predictive power of the scoring systems for DIC, although the accuracy of both systems remains to be established in prospective studies.

In conclusion, simple scoring systems for DIC employing readily available laboratory tests seem to be useful for confirming or rejecting a diagnosis of this condition. Prospective validation studies show that these algorithms are quite accurate and recent studies indicate that small modifications may improve their diagnostic accuracy even further. A caveat in the scoring algorithm is the fact that the test that is used as fibrin-related marker, which is mostly a D-dimer test, should be validated for its use in the diagnosis scoring system for DIC. The new international scoring system for DIC is a simple tool that may be helpful at the bedside but also for the use in clinical studies aimed at the improvement of the clinical management of patients with conditions known to be associated with DIC.

REFERENCES

Mediastinal emphysema complicating diabetic ketoacidosis: plea for conservative diagnostic approach

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ABSTRACT

Background: Spontaneous pneumomediastinum has been infrequently reported as a complication of diabetic ketoacidosis. Evidence-based guidelines are currently not available to help in choosing the best diagnostic approach.

Methods: We conducted a systematic review of the literature and looked for diagnostic clues that might indicate the need for a work-up to rule out oesophageal perforation.

Results: In all 56 published cases of spontaneous pneumomediastinum associated with diabetic ketoacidosis, the condition was self-limiting. We report one additional case of a 31-year-old female who presented with a spontaneous pneumomediastinum and also epidural pneumatosis, complicating diabetic ketoacidosis.

Conclusion: Important pathology, such as oesophageal rupture, was not detected in any of the reported cases, and we suggest a restrictive diagnostic work-up.

KEYWORDS

Diabetic ketoacidosis, epidural pneumatosis, pneumomediastinum

INTRODUCTION

Pneumomediastinum or mediastinal emphysema, which was first described by Hamman in 1937, is defined as the presence of gas within the mediastinum. It may result from direct trauma or rupture of the oesophagus, or mechanical ventilation (‘barotrauma’). Primary or spontaneous pneumomediastinum is believed to result from rupture of alveoli, following an activity that produces high intrathoracic pressure swings, such as labour, vomiting, coughing, sneezing or Valsalva manoeuvres. Diabetic ketoacidosis with acidotic (‘Kussmaul’) respiration and/or vomiting is one such condition. In a recent report, 51 cases were reviewed, including one case that was previously reported from the Netherlands. No guidelines are available to help in choosing the best diagnostic approach for patients presenting with diabetic ketoacidosis accompanied by pneumomediastinum.

METHODS

We searched MEDLINE and PubMed in English, Dutch, and German language publications, with the search strategy: ‘{pneumomediastinum OR (mediastin* AND emphysema)} in association with ‘diabetic ketoacidosis’. We also used the references of all reviews and relevant papers that we retrieved, cross-checking for double publications. Two investigators (RP and TW) independently studied all relevant abstracts. Demographic data, blood gas analysis results, and all other laboratory data were entered in a data sheet for analysis. In addition, we report one additional case not previously published.

RESULTS

Until 2004, 51 cases of pneumomediastinum in association with diabetic ketoacidosis and since then five more cases have been reported, including our patient who we describe in detail below. Of these, we could summarise the clinical and laboratory data of the 40 cases that were...
Results of the English, Dutch, and German literature (table 1). The mean age of these 40 evaluable patients was 41 years, and there were twice as many males as females. Not all features studied were available for all of the 40 patients. Oesophageal rupture was not detected in any of these 40 patients during clinical follow-up. Computed tomography (CT) studies were negative in all of the five patients who had this test, and oesophageal integrity was not impaired in any of the 13 patients who underwent contrast swallow studies.

CASE REPORT

A 31-year-old woman with type 1 diabetes mellitus had complaints compatible with gastroenteritis that initially subsided with antiemetics. When the vomiting recurred, diabetic ketoacidosis was suspected; she received additional short-acting insulin and was referred. She had pyrosis but no chest pain. She was on short-acting insulin three times daily before meals and long-acting insulin nocte, and an oral contraceptive. On admission, large tidal ventilations 20/min were noted; there was no smell of acetone. Her pulse was regular at 130 beats/min; blood pressure was 166/99 mmHg. No clinical signs indicating dehydration (i.e., dry arm pits, or reduced skin elasticity) were noted. Body temperature was 37.8°C. She had palpable skin crepitations in the supravacular fossae, left hemi-thorax and neck. Hamman’s sign, i.e. a crunching, popping noise over the cardiac apex and left sternal border, synchronous with each cardiac systole was present. Apart from modest abdominal tenderness, no other abnormalities were found. Laboratory investigations showed blood glucose 16.8 mmol/l. Arterial blood gas analysis demonstrated a pH 7.42, bicarbonate 14 mmol/l, pCO2 2.9 kPa, pO2 14.6 kPa and base excess -8.4 mmol/l without elevated lactate. Blood urea was elevated (16.1 mmol/l) and creatinine was normal (88 µmol/l), sodium 132 mmol/l, chloride was not measured so the anion gap could not be calculated, potassium 3.9 mmol/l, C-reactive protein slightly elevated (13 mg/l) and white blood cell count (WBC) normal (8.8 x 10^9/l). A urine pregnancy test was negative; ketone bodies were present in the urine, as evidenced by a qualitative dip-stick analysis. Chest X-ray showed subcutaneous as well as pericardial emphysema, confirmed by chest CT scanning, showing a minor pneumothorax, a normal oesophageal wall and interestingly, epidural pneumatosis. Oesophageal swallow examination the next day (water-soluble contrast solution) was normal.

<table>
<thead>
<tr>
<th>Patients analysed (n=40)</th>
<th>Recorded in (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean 41 (± SD 12)</td>
</tr>
<tr>
<td></td>
<td>Range 7-78</td>
</tr>
<tr>
<td>Female/male</td>
<td>13/27</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Present in 27</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>Present in 18</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>Mean 36.9 (± 0.9)</td>
</tr>
<tr>
<td></td>
<td>Range 34.2-37.8</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td>Mean 111 (± 0.9)</td>
</tr>
<tr>
<td></td>
<td>Range 92-160</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>Mean 120 (± 0.9)</td>
</tr>
<tr>
<td></td>
<td>Range 80-160</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>Mean 73 (± 0.9)</td>
</tr>
<tr>
<td></td>
<td>Range 40-99</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min)</td>
<td>Mean 35 (± 0.8)</td>
</tr>
<tr>
<td></td>
<td>Range 18-52</td>
</tr>
<tr>
<td>Hamman’s sign</td>
<td>Present in 22</td>
</tr>
<tr>
<td>pH</td>
<td>Mean 7.0 (± 0.14)</td>
</tr>
<tr>
<td></td>
<td>Range &lt;6.8-7.42</td>
</tr>
<tr>
<td>PaCO2 (kPa)</td>
<td>Mean 2.1 (± 0.9)</td>
</tr>
<tr>
<td></td>
<td>Range 0.6-3.6</td>
</tr>
<tr>
<td>Blood glucose concentration (mmol/l)</td>
<td>Mean 36.0 (± 15.2)</td>
</tr>
<tr>
<td></td>
<td>Range 13.8-87.4</td>
</tr>
<tr>
<td>WBC (x 10^9/l)</td>
<td>Mean 25.2 (± 8.9)</td>
</tr>
<tr>
<td></td>
<td>Range 8.8-42.2</td>
</tr>
<tr>
<td>CT scan</td>
<td>Epidural pneumatosis n=2</td>
</tr>
<tr>
<td>Oesophagus swallow study</td>
<td>Contrast leakage: none</td>
</tr>
<tr>
<td>Pneumothorax (chest X-ray)</td>
<td>Oesophageal rupture: none</td>
</tr>
</tbody>
</table>

intravenous insulin and fluid and potassium substitution, hyperglycaemia and metabolic derangements were readily corrected. Persistent pyrosis prompted an oesophago-gastroscopy that revealed grade D distal reflux oesophagitis, successfully treated with omeprazole. Five days later the chest X-ray had normalised, and she was discharged. A chest film was compatible with subcutaneous as well as pericardial emphysema (figure 1). CT scanning confirmed the presence of subcutaneous emphysema and demonstrated the presence of a pneumopericardium, pneumothorax and epidural pneumatoasis (figure 2).

**DISCUSSION**

Pneumomediastinum is a benign, self-limiting complication of diabetic ketoacidosis. Epidural pneumatoasis has only been reported once in association with diabetic ketoacidosis. However, it might be more common and perhaps went unnoticed before CT scanning became readily available. Apparently, vomiting may not explain all cases of pneumomediastinum. Acidothic (‘Kusmaul’) breathing alone may apparently induce transalveolar pressure swings that are sufficient to cause alveolar rupture. Chest discomfort (in 45%) may result from air collections in the mediastinum or pleural space. Three patients including ours had pneumothorax but none required pleural drainage. Acidotic (‘Kusmaul’) breathing alone may apparently induce transalveolar pressure swings that are sufficient to cause alveolar rupture. Chest discomfort (in 45%) may result from air collections in the mediastinum or pleural space. Three patients including ours had pneumothorax but none required pleural drainage. Air collections may appear at different anatomical sites depending on the site of alveolar rupture. Subpleural alveolar rupture may result in pneumothorax, and subcutaneous emphysema which is often observed in association with pneumothorax. Rupture adjacent to bronchovascular bundles may cause pneumomediastinum and pneumopericardium, entities frequently associated with pneumothorax. Epidural gas collections may result from gas passing from the posterior mediastinum through the intervertebral foramina into the epidural space. Severe persistent vomiting and chest pain suggests oesophageal rupture (Boerhaave syndrome). However, oesophageal rupture was not detected in any of the 40 cases of ketoacidosis-associated pneumomediastinum that we reviewed. Oesophageal rupture in this setting is unlikely. Spontaneous pneumomediastinum associated with conditions other than diabetic ketoacidosis also has a benign course. Most of the clinical signs are likely to have subsided by the time metabolic control has been achieved, and when patients are able to drink, we suggest that they are started on clear fluids first. Gastro-oesophageal endoscopy is only indicated when other pathologies are being considered. In our patient severe gastro-oesophageal reflux disease was diagnosed. Until perforation has been ruled out, endoscopy should not be performed. Oesophageal swallow imaging with water-soluble contrast solution is a safe procedure to rule out Boerhaave syndrome, provided that the patient is conscious.

**CONCLUSION**

Pneumomediastinum associated with diabetic ketoacidosis has a benign course and a restricted diagnostic approach is justified.
NOTE

This report reviews the literature, and reports one additional case that cannot be recognised from the case description; ethics clearance by IRB was waived. The patient however declared to us that she would be pleased if her case was reported in the literature.

REFERENCES

Liver transplantation: an update

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ABSTRACT

Liver transplantation has been an accepted treatment for end-stage liver disease since the 1980s. Currently it is a highly successful treatment for this indication. The aim of this review is to give a general update on recent developments in the field of liver transplantation. In the last decades considerable progress has been made in the care of liver transplant candidates and recipients. At present the one- and five-year patient survival rates are approximately 85 and 75%. The indications for liver transplantation are shifting and the number of absolute contraindications is decreasing. In the coming years, an increase in the number of transplant candidates can be expected. An important problem is the shortage of donor organs, for which many solutions are being explored. A recently introduced method for recipient selection is the MELD score using simple laboratory measurements. Perioperative care at the present time is characterised by a high degree of standardisation and rapidly declining blood loss during transplantation. Long-term care includes awareness and management of recurrent disease. Important causes of morbidity and mortality such as de novo malignancies and cardiovascular disease should be adequately screened for and managed. With the increasing success of liver transplantation, physicians should aim at reaching a normal life expectancy and quality of life for transplant recipients.

INTRODUCTION

The first report on attempts to transplant a liver in humans was by Starzl in 1963.1 In the following years liver transplantation developed from an experimental operation with very high mortality rates into a standardised procedure with rapidly decreasing perioperative mortality. This ultimately led to a statement from the National Institute of Health (NIH) in 1983 declaring liver transplantation as an accepted therapy for end-stage liver disease.2 Currently, liver transplantation is the treatment of choice for acute and chronic liver failure. Survival is excellent on both the short and long term, with patient survival rates of approximately 85% one year after surgery and 75% five years after transplantation (source: www.eltr.org). Survival figures from our centre are shown in figure 1. As can be seen in the figure, survival has improved markedly over recent decades. The two lines represent the survival of patients before and after the median date of our transplant programme. The first liver transplantation in the Netherlands was performed in Arnhem in the 1960s. The procedure, however, was not part of a formal transplant programme. Liver transplantation was first performed in Groningen in 1979. The University Hospital Groningen (currently University Medical Centre Groningen) pioneered...
this treatment in Europe with a few other centres. The final NIH declaration was based partly on data from the Groningen programme. Currently, three university medical centres are performing liver transplantations in the Netherlands: Rotterdam, Leiden and Groningen. There is a shared protocol for indication and selection of patients. In the recent decades there have been important developments in patient selection, perioperative care, and long-term follow-up of liver transplant recipients. The aim of this review is to give an update on the present state of liver transplantation in adults, and to highlight some recent developments on indications for transplantation, patient selection, perioperative care, immunosuppression and long-term management of liver transplant recipients.

**INDICATIONS AND CONTRAINDICATIONS FOR LIVER TRANSPLANTATION**

The most important indications for liver transplantation in Europe are viral hepatitis (24%), alcoholic liver disease (20%), cholestatic liver diseases (18%) and hepatocellular carcinoma (10%) (source: www.eltr.org). The indications in our centre are shown in figure 2. Throughout the years, a changing pattern of indications has been recognised. The number of patients transplanted for hepatitis C cirrhosis and alcoholic cirrhosis is increasing, and the number of patients with immune diseases such as primary biliary cirrhosis is decreasing.

For alcoholic disease, the prerequisites for transplantation in most centres are alcohol abstinence for at least six months and active treatment for alcohol dependency. In general, treatment for hepatitis C virus infection is not effective in the advanced stage of cirrhosis, with the consequence that the infection recurs in the transplanted liver. This often results in a recurrence of chronic hepatitis and gradual progression to cirrhosis at 10 to 15 years after transplantation. Patients with hepatitis B cirrhosis and high hepatitis B viraemia were not eligible for transplantation in the past because of the high risk of recurrence after transplantation with consequent rapid graft loss. Since the availability of antiviral medication, high viraemia is treatable and transplantation has become a more realistic option with excellent graft and patient survival that is even superior to that of many other indications. After transplantation, antiviral treatment, often including hepatitis B immunoglobulin, is continued to prevent recurrent infection.

About 10% of patients are transplanted because of acute liver failure. The main causes of acute liver failure are drug hepatotoxicity (mostly acetaminophen) and acute viral hepatitis. The waiting time for a donor liver and the threat of developing multiple organ failure and cerebral death during this time are of critical importance. The role of albumin and MARS dialysis (Molecular Adsorbent Recycling System) as a bridge to transplantation is under discussion and being investigated.

![Figure 2. Changing indications for liver transplantation at the University Medical Centre Groningen: before (n=247) and since (n=325) 1996](image-url)

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Primary hyperoxaluria is an inborn error of metabolism of the alanine:glyoxalate aminotransferase in the liver. The result is a systemic disease with loss of kidney function. Liver transplantation may halt further progression of the disease. Transplantation in an early stage may prevent the need for haemodialysis and kidney transplantation. At a later stage, when kidney failure has already developed, combined liver and kidney transplantation is the best option. Familial amyloidotic polyneuropathy is another example of a disease in which an inborn error of metabolism in the liver leads to systemic disease. In this case, mutant transthyretine production in the liver leads to amyloid depositions in the body. It is now known that in more advanced patients, cardiovascular amyloid may progress despite liver transplantation. Therefore, transplantation early in the course of disease now seems to be the best treatment option.5

Hepatocellular carcinoma is a well-recognised indication for transplantation when no other treatment options are available. Generally, only patients who meet the Milan criteria of a single tumour up to 5 cm or up to three tumours up to 3 cm, as determined by imaging studies,6 are approved by the transplant organisations in most countries. Discussion at present focuses on expansion of these strict criteria, as on the one hand the removed liver often shows more tumour lesions than expected, and on the other hand patients with somewhat larger lesions often do well. In clinical practice, long waiting times for a suitable donor liver play an important negative role and strategies for downsizing or (temporary) control of the tumour are increasingly being used. Local ablative therapy, using radiofrequency ablation (RFA), is currently the preferred therapy in our centre in this situation.

Graft failure with the need for retransplantation accounts for an increasing number of transplantations. Shortly after transplantation, this mainly concerns primary nonfunction and hepatic artery thrombosis, later biliary complications and recurrent hepatitis C can become indications for retransplantation.

Although there is no formal age limit for liver transplantation, most centres rarely transplant patients over 65 years of age. It has been shown that older recipients (over 60 years) have a significantly reduced survival, mainly due to the high incidence of malignancies.2,8 Until recently, infection with the human immunodeficiency virus (HIV) was considered an absolute contraindication to liver transplantation. Many HIV infected patients, however, are co-infected with hepatitis B or C, and viral hepatitis and cirrhosis are a significant cause of mortality in these patients.9,10 Also, the introduction of HAART (highly active antiretroviral therapy) has greatly improved survival in HIV-infected individuals. Currently, HIV infection is no longer an absolute contraindication for orthotopic liver transplantation (OLT), provided strict criteria for disease stage are fulfilled. Early results of OLT in HIV-positive patients are encouraging.11,12

Another development is the increasing number of patients transplanted with more than one organ. This can be done in patients with combined kidney/liver, intestine/liver or lung/liver failure.

In general, the past few years are characterised by an increasingly shorter list of absolute contraindications and a growing list of indications for liver transplantation.

SELECTION OF DONOR AND RECIPIENT

Changing donor characteristics

Worldwide, physicians are struggling with waiting list mortality and an increasing demand for donor livers. This situation is also present in the Netherlands as can be seen in figure 3. This has led to expanded criteria for donor livers, accepting organs from ‘compromised donors’. Where in previous decades many donors were young people dying of traumatic brain injury, currently over one third of donors are over 50 years of age.13 To expand the donor pool, livers with steatosis and livers from donors with malignancies or prolonged ICU stay are being used with variable success rates.14 The use of non-heart-beating donors (donation after cardiac death) may be a substantial source of donor organs. Transplantation using these grafts is unfortunately accompanied by increased rates of biliary strictures and early graft failure, leading to the need for retransplantation.15,16 One way to improve the outcome of transplantation with organs from compromised donors is the use of better preservation solutions or...
machine perfusion of the liver, providing hypothermic or possibly normothermic organ perfusion. These techniques are currently being tested for their value in clinical transplantation.77

Besides stretching donor criteria, other techniques have been used to expand the donor pool. For example, in some cases donor livers can be split into a right and left liver graft, with the potential to provide two patients with a donor organ.8,9 It should be noted, however, that partial liver grafts generally perform worse than whole liver grafts.89 Another option is to re-use the liver from patients undergoing liver transplantation for metabolic diseases such as familial amyloidotic polyneuropathy to transplant patients with cirrhotic liver disease.81

Live donor liver transplantation
A revolutionary way to expand the donor pool has been the use of partial liver grafts from live donors: live donor liver transplantation (LDLT). This procedure was pioneered in the late 1980s in children190 and subsequently developed into a practice used worldwide. LDLT is currently commonly performed in the United States, Europe and especially Asia, where whole liver grafts are rarely used. Reports on significant donor morbidity and mortality have, however, tempered initial enthusiasm. In 1996, 4% of liver transplantations in the USA were performed using a graft from a living donor (source: www.unos.org). In the Netherlands, live-donor liver transplantation has been performed in adults (Rotterdam) and children (Groningen) since 2004. In 2006 three LDLT procedures have been performed in the Netherlands (source: annual report Nederlandse Transplantatie Stichting 2006). Whether LDLT will be of growing importance in the Netherlands remains to be seen, and is also dependent on for example the effects of the MELD score on waiting list mortality and public opinion on LDLT.

Although all the attempts to increase the donor pool mentioned above are worth pursuing, probably none of them will prove sufficient to increase the number of donor livers. In addition, grafts from marginal donors and split livers most likely have a negative influence on recipient outcome. A potential method to minimise this influence may be to better match donor and recipient characteristics.83 Another possible solution may lie in changing legal issues regarding donorship and public awareness campaigns increasing the number of organ donors.

The MELD score for organ allocation
The Eurotransplant International Foundation is responsible for the mediation and allocation of organ donation procedures in Austria, Belgium, Germany, Luxembourg, the Netherlands, Slovenia and Croatia (candidate member). An important development in the allocation of donor organs has been the introduction of the MELD score (Model for End-stage Liver Disease).84 Originally developed to calculate the risk for survival after placement of a TIPS (transjugular intrahepatic portosystemic shunt), the MELD score proved to be a predictor of survival in various liver diseases. The score is obtained by a mathematical calculation using three widely available laboratory variables: international normalised ratio (INR), serum creatinine and serum bilirubin (MELD = 9.57 x loge (creatinine) + 3.78 x loge (total bilirubin) + 11.2 x loge (INR) + 6.43).

Since December 2006, Eurotransplant has been allocating livers by means of the MELD score. The MELD score was first used in the USA. In the late 1990s, when waiting list mortality was rapidly increasing in the USA, a different way to allocate organs was needed. Till that time, organs were allocated on the basis of both the severity of the liver disease as well as time spent on the waiting list. The rationale behind using the MELD score is the ‘sickest first’ policy, in which not the time on the waiting list but the mortality risk determines to whom an organ is allocated.85 After introduction of the MELD score in the USA waiting list mortality dropped substantially.86 MELD score is not applied in patients with fulminant hepatic failure. Modifications in organ allocations purely based on MELD are used in patients with metabolic disease and hepatocellular carcinoma, since the MELD score does not adequately reflect disease severity in these patients.

Developments in perioperative care and the surgical procedure
With the increasing number of liver transplantations performed, the surgical technique and perioperative care have developed towards standardised procedures and management. Two subjects will be discussed in more detail below: intraoperative blood loss and the surgical technique of the caval vein anastomosis.

Intraoperative blood loss
Blood loss during liver transplantation used to be one of the most important causes of perioperative death in the early days of transplantation. Although rarely so these days, increased blood loss and subsequent transfusions still contribute to postoperative infection,75 mortality88 and surgical reintervention.89 Interventions to reduce blood loss during OLT have been surgical, anaesthesiological and pharmacological.88 An important surgical contribution to minimise blood loss has been the implementation of the piggy-back technique (see below). The anaesthesiologist has a crucial role in correcting coagulation abnormalities with blood products, preventing hypothermia, correcting acidosis and maintenance of a low central venous pressure ensuring a low pressure in the

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hepatic veins, inferior vena cava, as well as the splanchic venous circulation. In recent years, many controversies have surrounded the use of pharmacological agents used to prevent or treat blood loss during OLT. Aprotinine, recombinant factor VIIa and tranexamic acid have been most widely studied. In selected cases it appears that these agents can contribute to a reduction in the need for blood products. With the use of the measures mentioned above, in our centre 40% of first adult liver transplantations are currently performed without any transfusion of red blood cells. The reduction in blood loss has also led to the successful transplantation of livers in Jehovah’s witnesses. Also in our centre Jehovah’s witnesses are no longer excluded from liver transplantation.

The caval vein anastomosis
Classically, the reimplantation of the donor liver in orthotopic liver transplantation is performed using an end-to-end anastomosis to re-attach the supra- and infra-hepatic vena cava of the donor and recipient. In recent years, the cava-sparing or piggy-back technique has become the standard. In this technique, the recipient’s retrohepatic inferior vena cava remains intact. The inferior vena cava of the donor liver is sutured in an end-to-side or side-to-side fashion to the vena cava of the recipient (figure 4). By using this technique, dissection of the retroperitoneum is avoided and only one caval anastomosis has to be made, resulting in less blood loss, a shorter anhepatic phase and less haemodynamic instability. The piggy-back technique has proven to be both safe and efficient.

**IMMUNOSUPPRESSION AFTER LIVER TRANSPLANTATION**

Solid organ transplantation was revolutionised by the introduction of cyclosporine as an immunosuppressant in the 1980s. After cyclosporine, a number of other drugs (tacrolimus, mycophenolate mofetil, sirolimus) were introduced expanding the possibilities for immunosuppression. Large series describing results from the previous years mention acute rejection in 40 to 60% of liver transplant patients. More recent data from the USA for 2003 show acute rejection in as few as 18% of patients (www.unos.org). Moderate to severe acute rejection has been described in up to 15% of transplants. The vast majority of patients can be treated satisfactorily with boluses of steroids. Chronic rejection is a rare event in liver transplantation, occurring in less than 5% of patients. On the long term, graft loss due to either acute or chronic rejection occurs in approximately 1% of liver transplant recipients. In the majority of liver transplant recipients, rejection is prevented by a combination of two or three different maintenance immunosuppressive drugs. The calcineurin inhibitors tacrolimus and cyclosporine are the mainstays of immunosuppression in liver transplantation. Over 95% of patients are discharged with a calcineurin inhibitor as a primary immunosuppressant, with tacrolimus being most frequently used (www.unos.org). In several analyses the superiority of tacrolimus over conventionally dosed cyclosporine with regards to the prevention of rejection has been shown. Steroids are still almost universally used after liver transplantation. There has been a trend towards a rapid steroid taper and steroid weaning shortly after transplantation. Currently, in the USA most patients are discharged with steroids, which are subsequently weaned in the following months, and eventually completely stopped in over 50% of patients (www.unos.org). Besides the particularly commonly used calcineurin inhibitors and steroids, antimetabolites (azathioprine or mycophenolate mofetil (MMF)) are also frequently used. UNOS data show that 60% of patients are discharged from the hospital on one of the two agents, with MMF being more frequently used. MMF is as safe as azathioprine but more effective in preventing acute rejection. An advantage of antimetabolites is their profile of side effects which is markedly different from calcineurin inhibitors, thus creating the possibility to reduce the calcineurin inhibitor dose and preventing or limiting side effects such as renal dysfunction, hypertension and hyperlipidaemia.

Drugs that are currently under investigation are the m-TOR inhibitor sirolimus and the related everolimus. Potential advantages of these drugs are their lack of nephrotoxicity and the antifibrotic and antineoplastic characteristics. Their clinical value still needs to be proven in larger studies, although present data show great potential. In general, one can say that currently the most important challenge with regards to immunosuppression in liver transplantation is not to find drugs that are more powerful, but drugs that are less harmful. In the

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*Figure 4. Piggy-back procedure*
meantime, the present availability of a wide spectrum of effective and specific immunosuppressive drugs allows individualised selection of drugs, thereby limiting serious side effects.

**BILIARY COMPLICATIONS AFTER LIVER TRANSPLANTATION**

Since the early days of liver transplantation, biliary complications have been an important source of morbidity, and in severe cases even loss of the graft or mortality. Despite great improvements in both surgical and medical management of liver transplant recipients, biliary complications are still common, occurring in 6 to 35% of patients. It appears that the biliary epithelium is much more susceptible to ischaemic injury than liver parenchyma and gross vascular structures.

The biliary anastomosis in liver transplantation is most commonly performed making an end-to-end anastomosis of the donor and recipient common bile duct (choledocho-choledochostomy or duct-to-duct anastomosis). The remainder of transplants are performed using a roux-en-Y anastomosis (hepaticojejunostomy), especially when the recipient bile duct is too short or unsuitable, i.e. in patients with primary sclerosing cholangitis.

Of the biliary complications, leakage of bile and strictures of the biliary tree are most commonly encountered. Bile leakage is usually seen shortly after transplantation and occurs in 5 to 7% of patients. It can occur at the site of the anastomosis, the cystic duct remnant or at the exit site of a biliary drain. The majority of cases can be successfully managed by placement of a stent through the sphincter of Oddi, reducing pressure in the common bile duct and preventing further leakage. Strictures of the biliary tree can be divided into anastomotic strictures (occurring at the site of the anastomosis of donor and recipients common bile duct) or nonanastomotic strictures (occurring elsewhere in the biliary system of the donor liver). Anastomotic strictures are usually due to fibrotic healing, and can be managed by ERCP in the vast majority of cases without any negative effects on the graft or patient survival. Nonanastomotic strictures (NAS) are of a much more complex nature. They occur in approximately 15% of cases and can present both early and late after transplantation. A radiological example of NAS is provided in figure 5. Their pathogenesis can be immunological, ischaemic or both. In a number of patients, NAS are due to recurrent primary sclerosing cholangitis. In severe cases, NAS can lead to progressive destruction of the biliary tree, causing recurrent bacterial cholangitis, biliary fibrosis or even cirrhosis. Treatment can be attempted with multiple sessions of dilatation and stenting of stenotic areas. A considerable number of patients, however, will need a retransplantation.

**LONG-TERM MANAGEMENT AND COMPLICATIONS AFTER LIVER TRANSPLANTATION**

With increasing survival after liver transplantation, research nowadays focuses more and more on the long-term management of liver transplant recipients, up to decades after their transplantation. Late mortality after liver transplantation (occurring >1 year after initial surgery) can be divided into liver-related and liver-unrelated causes, with liver-unrelated causes being responsible for approximately 60% of late mortality.

**Liver-related causes of morbidity and mortality: recurrence of disease**

Recurrence of hepatocellular carcinoma is especially common in patients with a poorly differentiated tumour or macroscopic vascular invasion. Surgical treatment of recurrent disease should be considered, but outcome is almost universally dismal. Recurrence of autoimmune diseases in an organ from a donor is immunologically intriguing. Diagnosis can be difficult due to other potential causes for graft dysfunction. Recurrence of an early stage of primary biliary cirrhosis may occur in a majority of patients transplanted for this indication in the long term, but seldom leads to cirrhosis. Surgical treatment of recurrent disease is seen in 22% of patients, and is treated as in nontransplant patients. Recurrence of primary sclerosing cholangitis occurs in about 11% of patients; diagnosis may be difficult because of overlap with nonanastomotic strictures from other causes.
Recurrence of hepatitis C is almost universally seen. It usually presents gradually in the postoperative course, but the fact that it can also progress rapidly leading to liver failure (fibrosing cholestatic hepatitis) is a well-known entity. During recent years, however, improved survival of patients transplanted for hepatitis C has been seen, with a ten-year patient survival of approximately 60%. Current, the treatment of recurrent HCV in the transplanted liver under investigation with some promising preliminary results.

Liver-unrelated causes of morbidity and mortality
Major liver-unrelated contributors to morbidity and mortality in long-term survivors after liver transplantation are de novo malignancies, cardiovascular disease, renal insufficiency and osteoporosis.

Malignancies
De novo malignancy has an incidence of 5 to 16% in different series. They significantly increase post-transplant mortality, with a calculated relative risk of cancer-related mortality of almost 3 compared with a nontransplant population. The risk for skin cancer shows the most marked increase, but also noncutaneous, solid organ cancer is more common than in the general population. Contributors to this increased risk are high-risk behaviour before transplantation (smoking, alcoholism) and the life-long use of immunosuppressive drugs. Consequently, post-transplant management should focus on the elimination of risk factors, as well as minimising the amount of immunosuppression. A screening protocol should be adopted for surveillance after liver transplantation, especially when the patient is a smoker, or has documented inflammatory bowel disease or previous skin cancer.

Cardiovascular disease
Almost all of the known risk factors for cardiovascular disease have an increased prevalence in liver transplant recipients: hypertension, diabetes, hyperlipidaemia occur in up to 75%, 15% and 40 to 60% of patients, respectively, long-term after transplantation. Also obesity is an increasing problem after liver transplantation, reported to occur in 30 to 70% of patients. This increase in risk factors is at least partly due to the continuous use of immunosuppressive drugs. This combined with the previously mentioned high-risk behaviour leads to a markedly increased risk for atherosclerosis and subsequent cardiovascular events. The relative risk for cardiovascular mortality in the liver transplant population has been calculated to be approximately 2.6 compared with age-matched controls. Vigorous screening for cardiovascular risk factors and aggressive management is justified in all liver transplant recipients.

Renal insufficiency
Impaired renal function before transplantation, chronic use of calcineurin inhibitors and hypertension probably all contribute to the increased risk for chronic renal disease after liver transplantation. The cumulative risk of renal failure has been described to be as high as 20% five years after transplantation. Strenuous management of hypertension and withdrawal or reduction of calcineurin inhibitors should be considered in an early stage.

Osteoporosis
The combination of low bone mineral density before transplantation due to hepatic osteodystrophy, malnutrition and inactivity and steroid use after transplantation puts the liver transplant recipient at increased risk for osteoporosis. In the earlier era of transplantation, osteoporotic fractures were a major cause of morbidity after liver transplantation. In the present era, with lower dosages of corticosteroids and the availability of bisphosphonates, we have the tools to prevent or treat bone disease both before and after transplantation.

Conclusion and future perspectives
Diseases of the liver are becoming increasingly common. In the near future, hepatitis C related morbidity will increase. With the worldwide epidemic of obesity, a vast increase in the number of patients with nonalcoholic fatty liver disease can be expected. Treatments for end-stage liver disease other than transplantation, such as antifibrotic agents, hepatocyte transplantation and ex-vivo liver support systems, are very promising but currently lack the efficacy to delay or replace transplantation. Considering the above, liver transplantation will continue to be the standard of care for patients with end-stage liver disease in the next decades.

Liver transplantation has become an incredibly successful therapy for end-stage liver disease. With the enormous progress that has been made in the past decades, the focus of research and patient care in liver transplantation has shifted. In the future, strategies to stimulate a form of ‘tolerance’ for the transplanted organ will continue to be searched for, with some promising developments already on the horizon. A great problem is the donor shortage, for which a solution still needs to be found. With the increasing long-term survival of liver transplant recipients, the aim of current practice should be to gain a normal life expectancy and quality of life for these patients. Prevention and management of cardiovascular mortality and malignancies long-term after successful transplantation deserves full attention.
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Verdonk, et al. Update on liver transplantation.


Reversible hypogammaglobulinaemia

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ABSTRACT

In this report we present four patients with reversible hypogammaglobulinaemia who required immunoglobulin substitution for several years. One patient had documented systemic lupus erythematosus (SLE), the other three patients had primary hypogammaglobulinaemia without known cause. Whereas the cessation of azathioprine therapy may have contributed to the recovery in the patient with SLE, the restoration of the immunoglobulin production in the other three patients occurred spontaneously.

All four patients were IgA deficient when the hypogammaglobulinaemia was first detected and remained so after IgM and IgG production had recovered. Two of the three patients who also had anti-IgA antibodies started to produce anti-IgA again after stopping the immunoglobulin substitution. We conclude that recovery of hypogammaglobulinaemia is possible but rare.

When recovery is suspected, we recommend that immunoglobulin substitution is stopped and the antibody response to vaccination is tested.

KEYWORDS

Primary hypogammaglobulinaemia, reversibility, secondary hypogammaglobulinaemia

INTRODUCTION

Hypogammaglobulinaemia is a manifestation of various primary immunodeficiency disorders (PIDs). Common variable immunodeficiency (CVID) is the most frequently occurring PID with hypogammaglobulinaemia. Other examples of PIDs with hypogammaglobulinaemia are transient hypogammaglobulinaemia of infancy, X-linked agammaglobulinaemia (XLA), severe combined immunodeficiency (SCID), X-linked hyper IgM syndrome (XHIM), and various types of autosomal recessive gene defects with disturbed B-cell maturation.1

Except for transient hypogammaglobulinaemia of infancy, primary hypogammaglobulinaemia is considered to be irreversible. Still, recovery has been reported in some CVID patients after acquisition of HIV infection.2-4 Secondary hypogammaglobulinaemia may resolve after elimination of the underlying cause. Song et al. reported a woman with reversible hypogammaglobulinaemia, the absence of B lymphocytes and systemic lupus erythematosus (SLE).5 In the present study we present one child with SLE who, similar to the case of Song et al., also showed a restoration of the number of B cells and immunoglobulin production. In addition, we describe three other patients, in whom the diagnosis of primary hypogammaglobulinaemia was made without identifying the underlying cause, who also manifested spontaneous recovery of gammaglobulin production.

CASE REPORTS

Case 1
The patient, a female born in 1989, presented at the age of two years with fever, walking disability and anisocoria. Viral encephalitis was suspected and treated with acyclovir. After this episode she developed muscular rigidity. Six months later, she suffered from an acute glomerulonephritis and thrombocytopenia (43 x 109/l). Antinuclear antibodies (ANA) and anti-dsDNA were positive. The diagnosis of SLE was made. At that time the immunoglobulin serum concentrations were IgG 12 g/l, IgM 1.83 g/l, and IgA <0.05 g/l. The glomerulonephritis was successfully treated with corticosteroids and azathioprine. In the following years, ANA and anti-dsDNA became negative. At the age of 13 years she suffered from a series of respiratory tract infections and severe hypogammaglobulinaemia was detected (IgG 1.82 g/l, IgM 0.01 g/l, IgA <0.05 g/l) with anti-IgA antibodies present (table 1). Circulating B cells were nearly absent, CD4 and CD8 positive T cells were normal. Bone marrow analysis revealed almost

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Table 1. Immunoglobulin levels in the patients over time

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<tr>
<td>Adults</td>
<td>11.58 ± 3.05 g/l</td>
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Values in italic immunoglobulin levels determined during immunoglobulin substitution.

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complete absence of mature B cells with a blockade before the Cylgu-positive-pre-B-cell stage (which means positive for cytoplasmatic μ heavy chains, a maturation defect). Subcutaneous immunoglobulin suppletion was started. Eighteen months after the start of substitution, the number of B cells in the blood returned to normal shortly after an episode of appendicitis and termination of the azathioprine. While the patient was still on stable substitution, IgG levels gradually rose to 11.20 g/l, IgM to 0.30 g/l but IgA remained absent (<0.05 g/l). There was
a normal spread of IgG subclasses. When subcutaneous immunoglobulin substitution was stopped, IgG levels remained normal and anti-IgA reappeared. Recently, our patient experienced an exacerbation of her SLE, for which she is treated with corticosteroids and methotrexate.

Case 2
A boy, born in 1998, presented at the age of four months with a progressive cough, tachypnoea, dyspnoea and failure to thrive. The diagnosis of Pneumocystis jirovecii infection was made after chest X-ray and bronchoalveolar lavage. This finding prompted analysis for an immunodeficiency. At presentation, serum IgG was 5.07 g/l, IgM 8.50 g/l, and IgA 0.08 g/l, with a rapid decrease within two months to IgG 3.52 g/l, IgM 0.19 g/l, and IgA undetectable (table 1). No anti-IgA-antibodies were found. Immunglobulin substitution was started successfully. From this point onwards, no major infections occurred. B cells identified by flow cytometry on CD19 and CD20, at the start of substitution, were absent. Bone marrow analysis at this time showed a relative accumulation of pre-B-I cells, normal pre-B-II cells and a decreased number of immature and mature B cells. T-cell analysis showed CD3+ cells 1.9 x 10^9/l, CD4+ cells 1.06 x 10^9/l, and CD8+ cells 0.15 x 10^9/l. CD40 ligand was normally expressed and T cells were also normal. No mutations in the BTK gene were found.

At the age of 2 years, the serum IgG concentrations had increased gradually to 11.1 g/l (table 1) and mature B cells became detectable in peripheral blood. Based on these findings it was decided to stop the subcutaneous immunoglobulin substitution under cover of prophylactic antibiotics that later had to be withdrawn because of allergic reactions to various antibiotics. Six weeks after withdrawal of the subcutaneous immunoglobulin substitution, the patient was vaccinated with the combined unconjugated diphtheria, tetanus and poliomyelitis vaccine (DTP) and with conjugated Haemophilus influenzae type-b (Hib) polysaccharide vaccine. The antibody response (IgG) to DTP was normal (diphtheria 0.66 IU/ml, tetanus 0.24 IU/ml, pneumococcal serotype 3: 9 U/ml, serotype 4: 4 U/ml, serogroup 9V: 2 U/ml) but to Hib no response (Hib IgM <1 U/ml, Hib IgG 3 U/ml) developed. This latter poor response to polysaccharide antigens and the problems with the antibiotic prophylaxis led to the decision to restart IgG substitution. When, at the age of three years, the serum IgG concentration had reached 15.5 g/l and IgM had increased to 0.56 g/l, suppletion of immunoglobulin was definitively stopped. Repeated DTP and Hib vaccination at this time resulted in a good response (diphtheria 2.45 IU/ml, tetanus 2.79 IU/ml, Hib IgM 47 U/ml, Hib IgG 131 U/ml). During follow-up to the age of eight years, serum IgG and IgM concentrations remained normal although IgA deficiency persisted. Major infections have not occurred.

Case 3
The patient is male, born in 1988, with mild mental retardation who presented with frequent upper respiratory tract infections and otitis media at the age of 4 years. Blood analysis showed concentrations for IgG of 0.36 g/l, IgM of 0.14 g/l and IgA <0.05 g/l (table 1). Antibodies against IgA were present. The number of B cells was normal (CD19 0.9 x 10^9/l), peripheral blood T cells were increased (CD3+ 6.0 x 10^9/l, CD4+ 2.86 x 10^9/l, and CD8+ 2.5 x 10^9/l). The patient was treated with weekly subcutaneous immunoglobulin suppletion, resulting in virtually complete disappearance of infections. At the age of 14 years, IgG levels (under substitution) were found to be 9.5 g/l. (Re)vaccination with DTP and Hib resulted in a good antibody response (diphtheria 2.61 IU/ml, tetanus 2.23 IU/ml, pneumococcal serotype 3: 32 U/ml, serotype 4: 9 U/ml, serogroup 9V: 11 U/ml, Hib IgM 13 U/ml, Hib IgG 107 U/ml). IgG suppletion was stopped at the age of 15 years. Infections did not recur and the IgG levels have remained normal. Anti-IgA antibodies reappeared.

Case 4
A woman, born in 1939, was referred in 1988 at the age of 49 years by a peripheral hospital with the diagnosis of CVID established two years earlier. She suffered from recurrent upper and lower respiratory tract infections. At that time, IgG was 2.7 g/l, IgM 0.26 g/l and IgA was undetectable with anti-IgA antibodies present. Two of the patient’s children were known to have selective IgA deficiency. Immunoglobulin supplementation was started in a dosage of 2.4 g IgG per week, subcutaneously because of the presence of anti-IgA antibodies. After initiation of immunoglobulin substitution the patient remained free of respiratory tract infections. At the age of 61 years, a remarkably high serum IgG concentration (7.82 g/l) was found, while she had not had the subcutaneous γ-globulin during the previous month. Vaccination with the 23-valent pneumococcal polysaccharide vaccine, two months after withdrawal of supplementation, showed a clear response (IgG antibody titre against serotype 3 increased in three weeks from 5 to 53 U/ml, the titre against serotype 4 increased from 12 to 264 U/ml) but the response to Hib vaccination was poor. A few months later she complained of progressive abdominal discomfort. Gastroscopy showed atrophic gastritis with metaplasia without evidence of Helicobacter pylori infection. A control endoscopy two months later revealed a poorly differentiated adenocarcinoma of the antrum stage pT3 N0 Mx. The carcinoma could be completely removed surgically. In the years after surgery, IgG and IgM concentrations remained normal without further supplementation. IgA remained deficient, but anti-IgA antibodies did not reappear. After more than five years of follow-up, the patient remained free of infections and the gastric cancer did not recur.
DISSCUSSION

In the current study we report four patients with reversible hypogammaglobulinaemia. One of them had SLE, in the other three patients the cause of the hypogammaglobulinaemia was unknown. These four patients belong to a population of approximately 200 patients with hypogammaglobulinaemia known in our combined paediatric and general internal clinical practice in a university hospital. Thus, recovery from hypogammaglobulinaemia can occur but is rare.

Hypogammaglobulinaemia may be found in patients with SLE, recovery has been described in one SLE patient. The pathogenesis of the development of hypogammaglobulinaemia in SLE is probably multifocal. In our patient (case 1), bone marrow analysis showed almost complete absence of mature B cells. Regarding the pathogenesis, a number of possibilities come to mind. First, autoantibodies against B lymphocytes (or relevant T lymphocytes) could play a role. This possibility was not checked in our patient. A second possibility is a defect in the intercellular signalling molecules, such as Fas or Fas-ligand (CD95). In MRL/lpr mice this defect leads to the development of SLE and hypogammaglobulinaemia. Autoimmune lymphoproliferative syndrome (ALPS) is also based on such a deficiency and can present with similar symptoms as SLE, such as glomerulonephritis or arthritis. However, a diagnostic criterion of ALPS is the presence of CD3+, CD4-, and CD8- lymphocytes, which was not the case in our patient. Fas was not measured in our patient. The spontaneous recovery of hypogammaglobulinaemia also argues against such a congenital defect. A third explanation may be the immunosuppressive treatment with azathioprine. When azathioprine was withdrawn in our patient, the B cells rapidly returned and the IgG level increased. Remarkably, during the period of hypogammaglobulinaemia, the SLE was in remission. This phenomenon, i.e. recovery of SLE during disappearance of autoantibodies, has been reported before. This is corroborated by our observation that the patient had a resurgence of her SLE, requiring resumption of therapy.

In the patient from case 3, we also considered the diagnosis of transient hypogammaglobulinaemia of infancy but rejected this diagnosis. In our patient the hypogammaglobulinaemia was very profound even at the age of 4 years and persisted for years, whereas in transient hypogammaglobulinaemia of infancy the decrease of immunoglobulins is less extreme and recovery is expected between 9 and 15 months of age, with a range of up to a maximum of 5 years of age. In the patients from case 3 and 4, we also considered the diagnosis CVID. Recovery from CVID is rare. Eisenstein and co-workers showed that culturing CVID B cells for several days in co-culture with activated normal allogenic T-cells with anti-CD40 and IL10 added, results in IgM and IgG immunoglobulin production was suspected when the IgG levels were measured under minimal immunoglobulin substitution. It is intriguing that at the same time, gastric cancer was diagnosed. The adequate responses to H1b and pneumococcal vaccines were found.

just before resection of the gastric cancer. One hypothesis is that the tumour played a causative role, for instance by producing a humoral factor counteracting the defect. Although we did not analyse the tumour tissue for such factors, this possibility is ruled out as the patient had a curative resection of the tumour with a follow-up of more then five years and persisting normal immunoglobulin levels. The reverse hypothesis that the hypogammaglobulinaemia was caused by the tumour is highly unlikely given the long history of CVID in this patient and the positive vaccination responses before surgery.

It is of interest to note that all our four patients were IgA deficient at presentation and remained so after recovery. In two of the three patients with anti-IgA antibodies at the moment of diagnosis, these antibodies became detectable again when immunoglobulin substitution was withdrawn. Therefore, it is unknown whether the absence of anti-IgA antibodies was explained by the masking effect of donor IgA or by the transient disappearance of the anti-IgA producing plasma cells.

In brief, as shown in the four patients described above, reversibility of hypogammaglobulinaemia can occur. When suspected, it is recommended to measure IgA and IgM, components that are not part of the immunoglobulin substitution. The next step would be to stop immunoglobulin substitution and to measure immunoglobulin concentrations after at least six weeks, followed by the measurement of the antibody response to vaccination with a protein and with a polysaccharide vaccine. When in doubt, one could test the response to vaccination with a neo-antigen (e.g. rabies vaccine), even during immunoglobulin substitution. Based on these findings a decision can be made to stop the substitution permanently.

REFERENCES

Intracranial multiple midline germinomas: is histological verification crucial for therapy?

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ABSTRACT

In this report we present two patients with intracranial multiple midline tumours in the suprasellar region and pineal gland. We postulate that in a patient with multiple midline tumours and normal values of the tumour markers human chorionic gonadotropin and α-fetoprotein in serum and cerebrospinal fluid, the only possible diagnosis is a germinoma. In such a situation no histological confirmation is required to start low-dose radiotherapy.

KEYWORDS

Diabetes insipidus, germ cell tumour, germinoma, radiotherapy

INTRODUCTION

Germinomas belong to the class of germ cell tumours that also comprises embryonal cell carcinoma, yolk sac tumour, teratoma (mature and immature) and choriocarcinoma. Extragonadal germ cell tumours typically arise in midline locations. The most common sites of origin in adults are the anterior mediastinum, retroperitoneum and the pineal and suprasellar regions of the brain. Primary intracranial germ cell tumours are rare, accounting for 2% of all primary intracranial brain tumours in adolescents and young adults, with a higher incidence in Japan. Approximately two-thirds of intracranial germ cell tumours are germinomas. Similar to their histological counterparts testicular seminoma and ovarian dysgerminoma, germinomas are extremely radiosensitive and have an excellent overall survival rate of 91 to 97%. Germ cell tumours may present with hypopituitarism in combination with neurological symptoms due to synchronous lesions in the pineal and suprasellar regions. These multiple midline lesions are almost exclusively germinomas. Because of the excellent prognosis of germinomas after radiotherapy, some feel that radiotherapy can be started without tissue diagnosis in the case of multiple tumours located in the midline of the brain, in the pineal and suprasellar regions. Whether or not this approach is justified will be discussed on the basis of our experience with two patients with intracranial multiple midline tumours.

CASE REPORTS

Case 1

A 16-year-old young lady presented with a five-month history of bilateral visual impairment followed by progressive headaches without nausea or vomiting. She did not complain of any other neurological symptoms. Visual acuity was 0.1 on the left and 0.8 on the right. Funduscopic examination revealed bilateral atrophy of the optic nerve. Additional neurological and general physical examination revealed no abnormalities. The differential diagnosis included mononeuritis optica and benign intracranial hypertension. Investigation of the cerebrospinal fluid (CSF) was unremarkable. Methylprednisolone was started at 1000 mg/daily on three consecutive days without effect. Because of positive Borrelia serology, chronic Lyme disease was suspected and she was treated with ceftriaxone intravenously, again with no effect. A few months later she developed further visual impairment. At that time, she complained of polyuria and polydipsia. Diabetes insipidus was confirmed by a thirst test. Further endocrinological testing showed panhypopituitarism. A magnetic resonance imaging (MRI) scan showed a thickened pituitary stalk and a mass in the pineal gland (figure 1A). Hydrocephalus
van Battum, et al. Multiple midline germinomas. was not present. CSF cytology showed lymphocytosis, monocytosis and tumour cells with immunohistochemical expression of cytokeratin (MNF 116). No α-fetoprotein or human chorionic gonadotropin (hCG) could be detected in the CSF.

A stereotactic biopsy of the pineal region was performed. Histological examination of the tissue was compatible with germinoma.

The patient received craniospinal radiotherapy to a dose of 19.8 Gy in 12 fractions, with an additional dose on the pituitary stalk and pineal gland of 21 Gy in 20 fractions. Visual acuity improved gradually. MRI scans of the brain at 3, 6 and 12 months after radiotherapy revealed that the abnormalities at the pituitary stalk and pineal gland had disappeared (figure 1B). At present she is doing well on full hormone replacement therapy. The visual acuity in both eyes is normal.

Figure 1A. T1-weighted Gd-enhanced MRI scan in patient 1 shows lesions in the suprasellar and pineal regions

Case 2

A 23-year-old man was referred to our hospital because of an 18-month history of central diabetes insipidus for which he was treated with nasal desmopressin. MRI scan of the pituitary gland was judged as normal. Six months before referral he complained of fatigue, weakness and erectile dysfunction. He did not complain of headaches or any other neurological symptoms. Physical examination as well as visual acuity were normal. Evaluation of pituitary function revealed panhypopituitarism and multiple midline lesions was considered compatible with the diagnosis of germinoma. For this reason no biopsy was performed. The patient received craniospinal radiotherapy to a dose of 24 Gy in 12 fractions and an additional dose to the tumours of 16 Gy in 8 fractions. MRI scans of the brain 1, 3 and 9 months after radiotherapy were normal (figure 2B).

Figure 2A. T1-weighted Gd-enhanced MRI scan in patient 2 shows lesions in the suprasellar and pineal regions

DISCUSSION

In this report we present two patients with intracranial multiple midline germinomas in the suprasellar region and pineal gland. In one of the patients the diagnosis was confirmed by histological examination of a biopsy taken from the pineal tumour. In the other patient the diagnosis was made on the basis of the clinical picture and the demonstration of multiple tumours in the midline region with MRI. This diagnosis was not verified by histology. In both cases, the tumours in both regions disappeared after irradiation with a dose lower than usual for intracranial tumours. No recurrence developed during follow-up for more than two years. These case histories raise two questions. Can a diagnosis of multiple midline germinomas be made on the basis of a typical clinical presentation only without histological verification and is a lower dose of radiation than usual for brain tumours indeed justified?

The presenting signs and symptoms of intracranial germinomas depend on the location of the tumour. Intracranial germinomas favour midline structures such as the suprasellar and pineal regions. A suprasellar lesion commonly presents with visual field defects due to compression of the optic chiasm, diabetes insipidus and other signs of hypothalamic-pituitary dysfunction. A lesion in the pineal gland usually presents with neurological dysfunction caused by intracranial hypertension due to direct invasion or obstruction of the CSF outflow.
including headaches, vision abnormalities, papiledema, ataxia, loss of upward gaze, Parinaud syndrome, tremor and altered pupillary reflexes. The differential diagnosis of suprasellar tumours comprises craniopharyngeoma, sarcoidosis, germ cell tumour, histiocytosis X and haemochromatosis. The most common tumours in the pineal region are germ cell tumours and parenchymal tumours such as pineocytoma and pineoblastoma. On the basis of these differential diagnoses of tumours in the suprasellar and pineal regions, the only possible diagnosis in case of multiple midline tumours is a germ cell tumour. Other abnormalities that can occur in the suprasellar region do not occur in the pineal region and vice versa.

Germ cell tumours can be classified according to their histological picture into pure germinoma, teratoma, embryonal cell carcinoma, yolk sac tumour and choriocarcinoma. The last three types of tumours usually constitute elements of mixed germ cell tumours. Intracranial germ cell tumours contain immunohistochemical features similar to those of gonadal germ cell tumours. These involve hCG, which is present in embryonal cell carcinoma, choriocarcinoma and mixed forms of these, and α-fetoprotein, which is also present in embryonal cell carcinoma as well as in teratoma and yolk sac tumours. These tumour products can also be detected in serum or CSF and are an adjunct to the diagnosis of a germ cell tumour and the prediction of tumour histology. A pure germinoma may contain hCG, but this is usually not the case; α-fetoprotein is not found in pure germinomas. So, in case of intracranial multiple midline tumours with normal values of the tumour markers hCG and α-fetoprotein in serum and CSF the only possible diagnosis is a germinoma. We feel that under such circumstances no histology is required to confirm this diagnosis. This suggestion is in line with published reports of multiple midline tumours in which biopsy revealed the histological picture of germinoma in all cases with normal tumour markers. On the other hand if both hCG and α-fetoprotein are elevated in serum or CSF the only diagnosis is embryonal cell carcinoma. In such a situation a biopsy is not needed either. In the case of elevation of either hCG or α-fetoprotein, there is a differential diagnosis as summarised in Table 1, necessitating biopsy for histological conformation.

In the first case in this report multiple midline tumours were found which, on the basis of the absence of tumour markers, were expected to be germinomas. The CSF, however, was suspicious for malignancy with lymphocytes positive for cytokeratin, indicating cells of epithelial origin and therefore a biopsy was performed to exclude other tumours than germinoma. Histology, however, showed a histological picture typical for a germinoma. In hindsight, one may wonder whether a biopsy was indicated in this patient, as mentioned before, as in the case of multiple midline tumours without tumour markers the chance of finding a tumour other than a germinoma is less than the risk of a biopsy. In the second patient, a germinoma was considered because of the multiple midline localisations and the absence of tumour markers in serum and CSF and the lack of other abnormalities in the CSF. For the reasons outlined before, a biopsy was therefore not considered necessary to establish the diagnosis and institute radiotherapy. Germinomas are highly sensitive to radiotherapy and survival rates vary between 91 and 97%. Lower dose (25 Gy and a total tumour volume dose of up to 45 Gy) given to the craniospinal axis produces disease-free survival and overall survival equivalent to those seen with higher doses of radiotherapy. Whether or not to radiate the spinal cord depends on the presence of tumour markers in the CSF. If elevated tumour markers are found in the CSF, which may be a sign of dissemination, spinal irradiation is necessary. In other circumstances whole brain radiation is effective in preventing intracranial tumour relapse. The reaction to radiotherapy supports the diagnosis: the tumours disappear soon after therapy. This was also the case in our patients. No recurrence occurred during follow-up. This again supports the diagnosis of germinoma as another course would be expected in other types of germ cell tumours after a radiotherapeutic approach.

**CONCLUSION**

In this report we present two cases of typical multiple midline germinomas. The multiple midline localisations, signs and symptoms of chiasma field defects, pituitary dysfunction and neurological dysfunction favour the diagnosis of pure germinoma. The absence of tumour markers in serum and CSF justifies blind treatment with radiotherapy. Because of the high radiosensitivity of germinomas, low-dose radiotherapy can be used, which is relevant for long-term morbidity as these types of tumours usually arise at a rather young age.

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**Table 1. Differential diagnosis of germ cell tumours in relation to tumour markers**

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</tr>
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hCG = human chorionic gonadotropin; α-fetoprotein = α-fetoprotein
REFERENCES


Van Battum, et al. Multiple midline germinomas.
CASE REPORT

Interstitial lung disease as the first manifestation of systemic sclerosis

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ABSTRACT

We describe three patients with progressive fibrosing interstitial lung disease (ILD) as the first and only manifestation of systemic sclerosis. In one patient the presence of anti-Scl-70 autoantibodies suggested systemic sclerosis to be the underlying cause of the disease. In the two other subjects, however, anti-Scl-70 antibodies were negative. In these patients the lung disease preceded other manifestations of systemic sclerosis by several years. Diagnosis, prognosis and treatment of systemic sclerosis-associated ILD is discussed.

KEYWORDS

Interstitial lung disease, scleroderma sine scleroderma, systemic sclerosis

INTRODUCTION

Idiopathic interstitial pneumonia (IIP) comprises a group of disorders of unknown aetiology, histopathologically characterised by a variable pattern of inflammation and/or fibrosis of the pulmonary interstitium. Various clinical entities, each of which defined by a specific histopathological pattern, are recognised.¹ Idiopathic pulmonary fibrosis (IPF) and (fibrotic) nonspecific interstitial pneumonia (NSIP) account for approximately 80% of IIP cases.¹ Histopathologically, IPF is characterised by a usual interstitial pneumonia (UIP) pattern and NSIP by a nonspecific interstitial pneumonia pattern.²-⁶ The histopathological hallmark of UIP is the heterogeneous appearance at low magnification with alternating areas of normal lung, interstitial inflammation, fibrosis and honeycomb changes. Moreover, characteristic foci of proliferating fibroblasts are a consistent finding. In contrast, the main histopathological feature of NSIP is the homogeneous appearance of either inflammation (cellular type NSIP) or fibrosis (fibrotic type NSIP). Although the process may be patchy with intervening areas of unaffected lung, the observed changes in NSIP are temporally uniform. Although the prognosis of both forms of IIP is still poor, the prognosis in fibrotic NSIP patients is significantly better than in IPF.²-⁶ Interstitial lung diseases, histopathologically indistinguishable from IIP, can also be observed as pulmonary manifestation of various collagen vascular diseases (CVD).² In most of these patients a fibrotic NSIP pattern is observed; however, a UIP pattern can also be present.³-⁵ The incidence of interstitial lung disease (ILD) differs among the various CVD. In systemic sclerosis, it can be observed in the majority of patients during the course of the disease²⁰ whereas, in systemic lupus erythematosus it is observed in a minority of patients only.¹¹ Moreover, in some CVD, ILD may be the first manifestation of the disease. In particular, in patients with polymyositis dermatomyositis and rheumatoid arthritis, the interstitial lung disease may precede the other manifestations by several years.²,ⁱ₂,¹³ Interstitial lung disease as a first manifestation of disease in systemic sclerosis, however, is extremely rare, and was previously reported to be associated with the presence of autoantibodies against topoisomerase I (anti-Scl-70 antibodies).¹⁴-¹⁵ In most cases of systemic sclerosis, however, lung involvement is observed relatively late in the course of the disease.¹⁶,¹⁷ In this paper we describe three patients with ILD as the first manifestation of disease in systemic sclerosis. Moreover, diagnosis, prognosis and treatment of systemic sclerosis-associated ILD are discussed.
CASE REPORTS

Case 1
A 59-year-old man was admitted to our hospital in 1999 because of sudden onset chest pain and high fever. He also suffered from progressive dyspnoea on exertion that had started two months prior to admission. He was a nonsmoker and he had no previous history of documented lung disease. On physical examination, Velcro-like crackles were heard at both lung bases; he showed no signs of heart failure. Physical examination was otherwise unremarkable. Laboratory tests revealed an erythrocyte sedimentation rate of 70 mm within the first hour; antinuclear factor (ANF) was positive, while anti-DNA antibodies were absent. Chest X-ray revealed signs of increased interstitial attenuation. Contrast-enhanced computed tomography (CT) revealed a pulmonary embolism in the left upper lobe. High resolution (HR) CT confirmed the presence of a bilateral interstitial lung disease with ground glass attenuation. He was treated with intravenous heparin and broad-spectrum antibiotics. Sputum and blood cultures remained negative. By serology, viral and atypical infections were excluded. HIV infection was also ruled out. At that stage, anti-Scl-70 antibodies turned out to be positive. So, a diagnosis of a fibrosing ILD (probably NSIP) of unknown origin was made; in view of the anti-Scl-70 antibodies, however, the most likely diagnosis was systemic sclerosis sine scleroderma. He was treated with corticosteroids (prednisone 1 mg/kg), whereupon his clinical condition gradually improved. After discharge, during follow-up at the outpatient clinic over the next three months, his hands became diffusely swollen and the skin thickened. He developed Raynaud’s phenomenon, started to complain about difficulties in swallowing food and showed signs of sclerodactyly. On the chest X-ray, the ILD was progressive. Taken together, the diagnosis of limited scleroderma was made with ILD as its first manifestation. Because of progression of the ILD, he was additionally treated with azathioprine and has been stable since.

Case 2
In 1998 the second patient, a female from Afghanistan aged 32 years, was referred to our hospital for further evaluation of a gradually progressive ILD. Her clinical history started in 1996. A chest X-ray, which was performed because of nonspecific, short-lasting right-sided knee pain, revealed diffuse interstitial abnormalities in both lungs. The patient was an active smoker but did not have any pulmonary symptoms. During the wintertime, however, she had complaints suggestive of Raynaud’s phenomenon. Already in 1996, HR-CT revealed a fibrosing ILD with reticular abnormalities with traction bronchiectasis and ground glass attenuation with a lower lobe predominance (figures 1 and 2). During follow-up, progression of disease was documented, and she started to suffer from shortness of breath. Pulmonary function tests showed decreased lung volumes and a decreased carbon monoxide diffusion capacity. A video-assisted thoracoscopic lung biopsy was performed. The biopsies showed a UIP pattern, so the clinical diagnosis of IPF was made. Infection, including tuberculosis, was ruled out. At that time, besides the possible Raynaud’s phenomenon, there were no clinical signs of any systemic disease. She was treated with high-dose intravenous methylprednisolone. Her symptoms decreased and both radiologically, as well as functionally, a significant improvement was observed. She was subsequently treated with a maintenance dose of 10 to 20 mg of prednisone daily and was stable over the next four years. Because of the
Raynaud’s phenomenon and her young age, we were aware of the fact that a CVD might be the underlying cause of the ILD. Rheumatoid factor was positive (20 kU/l), however, antinuclear antibodies (ANA), anti-Scl-70 and anticentromere antibodies (ACA) were repeatedly negative. In 2003, almost five years after the initial presentation, more clinical signs of systemic sclerosis appeared. Her skin thickened, she developed telangiectasias and she started to complain about stiffness of her hands, which became diffusely swollen. She developed sclerodactyilia and passage problems of the oesophagus. After being stable for several years, also the pulmonary symptoms increased, and both lung function tests as well as HR-CT scanning showed progression of disease. She was treated with intermittent intravenous cyclophosphamide, and has been clinically stable since. Upon treatment with cyclophosphamide the swelling of her hands disappeared. In 2005, nine years after the initial presentation, anti-Scl-70 antibodies were detected for the first time.

**Case 3**

The third patient, a 35-year-old female from Morocco, was referred to our hospital in 1998, with coughing and shortness of breath, which she had been suffering from for the last four years. On physical examination, Velcro-like crackles were heard over both lung bases. Chest X-ray revealed interstitial abnormalities as well as bronchiectases. HR-CT showed massive destruction of the lung architecture with signs of fibrosis (honeycombing), traction bronchiectasis and superposed diffuse ground glass attenuation. Repeated sputum cultures demonstrated colonisation with *Pseudomonas aeruginosa*. Lung function tests showed a severely decreased vital capacity (25% of the predicted value) and a severely decreased carbon monoxide diffusion capacity (16% of the predicted value). Additional examination, including bronchoscopy with transbronchial biopsies and extensive autoimmune serology (including ANA, extractable nuclear antigen (ENA) and rheumatoid factor), failed to clarify the diagnosis. Tuberculin skin testing was negative, and additional sputum cultures ruled out active tuberculosis.

At that stage, it was concluded that she was suffering from a nonclassifiable fibrotic ILD with severe restriction and hypoxaemia. In view of the fact that the patient deteriorated during admission, she was treated with high-dose prednisone (60 mg daily), after which her clinical condition improved, and she could be dismissed from the hospital. Two years after the initial presentation, the patient developed signs of sclerodactylia and telangiectasias. Serology was still negative for (anti-Scl-70 or anticentromere) autoantibodies. She was clinically diagnosed as suffering from limited scleroderma, with a fibrosing ILD as its first manifestation. She was turned down for lung transplantation. Ultimately, she died due to recurrent infections with multiresistant *P. aeruginosa*.

**DISCUSSION**

In this report we describe three patients with systemic sclerosis presenting with a progressive fibrosing interstitial lung disease as the first and only manifestation of disease. In the first patient the presence of anti-Scl-70 autoantibodies suggested systemic sclerosis to be the underlying cause of disease. In the two other subjects, however, anti-Scl-70 antibodies were negative. In these two patients the lung disease preceded other manifestations of systemic sclerosis by several years.

During the course of systemic sclerosis, pulmonary involvement can be observed in most patients. In fact, based upon autopsy studies, ILD can be demonstrated in virtually all patients, and it is observed in both limited and diffuse systemic sclerosis.\(^9,10,18-20\) Moreover, pulmonary disease is the leading cause of death in patients with systemic sclerosis.\(^9,24\) Early recognition of ILD is mandatory since symptoms will occur relatively late in the course of the disease. At that stage the patients may suffer from already severely impaired lung function due to irreversible interstitial fibrosis.

Establishing the diagnosis of ILD in patients with documented systemic sclerosis depends on several diagnostic tests. HR-CT is a widely accepted diagnostic tool to detect interstitial lung disease, and has been proven to be highly superior to the chest X-ray.\(^17,41,44\) Lung function tests, in particular the diffusion capacity for carbon monoxide, are simple and sensitive tests that may suggest the presence of pulmonary involvement. These tests can be performed routinely during the follow-up of patients.\(^27,97\) In addition, these tests can be used to monitor the effect of medical intervention. However, although a normal pulmonary function practically rules out the presence of ILD, an abnormal lung function has relatively low specificity since multiple factors can be involved in systemic sclerosis.

In a patient presenting with ILD, the presence of Raynaud’s phenomenon\(^18\) or positive autoantibodies, such as anti-Scl-70, anti-Jo-1 or rheumatoid factor (RF), may suggest a CVD to be the underlying cause of disease. However, the sensitivity of autoantibodies is low. Only 20 to 30% of patients with systemic sclerosis have anti-Scl-70 antibodies,\(^10\) and even in proven systemic sclerosis with ILD, anti-Scl-70 is absent in ~50% of cases. ACA are reported to be present in 20 to 60% of patients with systemic sclerosis.\(^29\) The presence of ACA in these patients is associated with a reduced frequency of ILD.\(^12,31\) These patients, however, have an increased risk of developing pulmonary arterial hypertension.\(^10,31\) On the other hand, in IIP a positive ANF or RF is present in 10 to 20% of cases without any evidence for a CVD during many years of follow-up. Histopathologically, two patterns of ILD can be observed in systemic sclerosis. UIP is observed in ~20%, and NSIP in ~80% of patients.\(^9,9,18\) In contrast to idiopathic UIP...
and NSIP, prognosis of systemic sclerosis-associated UIP and NSIP is similar. Moreover, survival in patients with systemic sclerosis-associated ILD is significantly better than in idiopathic UIP and NSIP. A number of drugs have been used for the treatment of systemic sclerosis-associated ILD, but none have proven effective. Based upon several retrospective studies only cyclophosphamide appeared promising, and was therefore adopted by most physicians, with or without low-dose prednisone, as the therapy of choice to slow down the rate of decline in these patients. The role of corticosteroids is still under debate; however, high-dose corticosteroids, as used in our patients according to idiopathic ILD treatment guidelines, have been reported to be associated with an increased risk for scleroderma renal crisis, and should not be used in these patients. Recently, two randomised, placebo-controlled trials with cyclophosphamide were published. One year of oral cyclophosphamide in systemic sclerosis-associated ILD was shown to have a significant but modest effect of life. In the second study, patients were randomised to receive low-dose prednisone and six-monthly infusions of cyclophosphamide followed by oral azathioprine or placebo. Although, probably due to lack of power, this trial failed to show a significant difference between treatment and placebo, there was a trend (p=0.08) toward statistical significance between the groups in one primary endpoint, i.e. forced vital capacity.

**CONCLUSION**

ILD as the first and only presentation of systemic sclerosis is extremely rare. However, it should be considered in patients with positive ANA and/or Raynaud’s phenomenon at presentation. In patients with systemic sclerosis-associated ILD, cyclophosphamide with or without low-dose prednisone should be considered to slow down the rate of decline and to preclude irreversible damage to the pulmonary parenchyma.

**REFERENCES**


A patient with hyperglycaemia and normal HbA\textsubscript{IC} due to impaired glycation

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ABSTRACT

A diabetic Caucasian woman presented with discrepantly low HbA\textsubscript{IC} values compared with her glycaemia. High-performance liquid chromatography (HPLC) analysis disclosed 80% HbA and 20% HbI Philadelphia (\textit{\textalpha}2 lys \textrightarrow glut). The calculated glycosylation gap from the fructosamine level was 1.2%. The haemoglobin \textalpha/\textbeta glycation ratios, as measured by electron spray ionisation mass spectroscopy (ESI-MS), for the patient and her three children also carrying the mutation were decreased by values of 0.56 and 0.51, 0.50 and 0.49, respectively (reference value 0.66).

KEYWORDS

Haemoglobinopathy, Hb Philadelphia, HbA\textsubscript{IC}, glycation

INTRODUCTION

The measurement of glycohaemoglobin (glyHb or HbA\textsubscript{IC}) serves as a powerful tool in the evaluation and management of patients with diabetes mellitus. In 1969, Rahbar accidentally observed the presence of an increased percentage of glycohaemoglobin (glyHb or HbA\textsubscript{IC}) in the blood of diabetic patients.\textsuperscript{1} Trivelli used this phenomenon as an indicator of long-term glycaemic control as it reflects blood glucose levels over the preceding six to eight weeks.\textsuperscript{2} Subsequently, this measurement was adopted by clinicians worldwide. HbA\textsubscript{IC} levels correlate well with the risk of development of chronic complications.\textsuperscript{3,4} Mean HbA\textsubscript{IC} levels of a hospital or practice are increasingly being used to assess quality of care and as a benchmark parameter. Knowledge of sources of variations in HbA\textsubscript{IC}, analytical or biological, is needed for correct interpretation.

CASE REPORT

A 77-year-old woman presented with a consistently discrepantly low HbA\textsubscript{IC} (5.8%) compared with her fasting blood glucose levels (\textit{table 1}). A random glucose day curve revealed a fasting blood glucose of 14.2, a postprandial value of 13.2 and a pre-dinner value of 8.2 mmol/l. For the last 20 years she had suffered from diabetes mellitus complicated by a mild nonproliferative retinopathy. Her current treatment consisted of a carbohydrate spread diet and metformin 500 mg/daily and glibenclamide 5 mg three times/day. Other medication included verapamil 240 mg/daily and aspirin 80 mg/daily. On physical examination her weight was 56 kg, height 1.55 m, body...
mass index 23 and office blood pressure 160/80 mmHg. Protective sensibility of her feet was intact. Laboratory investigations showed neither anaemia nor haemolysis (Hb 8.4 mmol/l, reticulocytes 106/μl, bilirubin 11 μmol/l, lactate dehydrogenase 343 U/l and haptoglobin 1.3 g/l) and normal renal function (creatinine 84 μmol/l and albuminuria 6 mg/24 h). Continuous 24-hour blood glucose monitoring ruled out hypoglycaemia and showed a mean blood glucose concentration of 9.0 mmol/l (figure 1). Fructosamine was 318 μmol/l (reference range 191-288 μmol/l), measured with a spectrophotometric assay (nitroblue tetrazolium (NBT) assay, Roche®). HbA1c measured with a routine turbidimetric immunoassay (Tina-quant, Roche®) and with high-performance liquid chromatography (HPLC) resulted in comparable values, but the latter method disclosed a haemoglobin variant consisting of 80% HbA and 20% HbI. DNA sequencing showed an AAG → GAG transition on codon 16 of the α2 gene leading to a substitution of lysine by a glutaminic acid molecule (α16 lys → glut, HbI Philadelphia). Three nondiabetic children of the patient were heterozygous for HbI Philadelphia and had fasting glucose concentrations (and HbA1c %) of 5.4 mmol/l (5.4%), 4.9 (5.2%) and 5.1 (5.5%) respectively. The α/β glycation ratios for the patient and her three children measured by electron spray ionisation mass spectrometry (ESI-MS) were 0.56 and 0.51, 0.50 and 0.49, respectively (reference value 0.66).6

**DISCUSSION**

HbA1c is a stable minor haemoglobin variant originally identified by separation of haemoglobin using cation exchange chromatography. It is mainly composed of glycohaemoglobin primarily glycated at the valine (position 1) of the N-terminal β-chain. However other amino-acids in the haemoglobin molecule can bind glucose. The ε-amino group of lysine at position 16 on the α chain is the second preferred site for glycation. This patient's haemoglobin is mutated precisely at this position where a lysine is exchanged for a glutaminic-acid residue, thus reducing the possible glycation sites which leads to less glycation. Glycation can be measured separately at the α and β chains by electron spray ionisation mass spectrometry (ESI-MS). The mean α/β glycation ratio was 0.66 in a large group (n=1022) of diabetic patients.6 Both

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### Table 1. Review of fasting blood glucose and HbA1c values in the years before presentation

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<td>5.7</td>
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**Figure 1. Continuous 24 hour blood glucose monitoring profiles**

![Continuous 24 hour blood glucose monitoring profiles](image-url)
the patient and her three children have α/β glycation ratios lower than 0.66 suggesting an effect of the mutation on the glycation process.

HbA1c values have a considerable biological variation when tested in patients with a comparable rate of glycaemic control suggesting the existence of slow and rapid glycation.2,8 Cohen et al. studied this phenomenon and developed a measure of discordance between the actually measured and the predicted HbA1c values from fructosamine (HbA1c = 0.017 x fructosamine (μM) + 1.61): the glycosylation gap.9 Applying this formula, the predicted HbA1c value of the discussed patient is 7.0%. With a measured value of 5.8% the resulting gap amounts to 1.2% pointing to impaired glycation.

The low HbA1c value in our patient is not explained by anaemia or haemolysis but there might be a shorter lifespan of erythrocytes containing the mutant haemoglobin, aggravated by hyperglycaemia, which is not expressed in the routine clinical parameters of haemolysis.10 In theory a chemical interference of the glycation process of the mutant haemoglobin by medication is possible. In vitro and animal studies report inhibition of glycation by metformin and aspirin.11,12 Her three children carrying the haemoglobin variant have seemingly normal HbA1c values in agreement with their normal blood glucose levels. Why don’t they have lower HbA1c values? Maybe glycation of the haemoglobin variant proceeds normally with euglycaemia but is slower when hyperglycaemia is present (glycaemia-dependent kinetics).13

When Hb Philadelphia leads to impaired glycation, a difference in the concentration of HbA1c can be expected between the amount measured by an immunometric method, which specifically measures glycation at the N-terminal valine of the β chain, and the amount measured by HPLC, measuring total glycation on both α and β chains. This small difference is, however, not detectable with routine assay methods. The rate of glycation can be measured experimentally, e.g. as reported in the case of the haemoglobin variant Hb Görwihl (αβ, 5 (A2) Pro→Ala) which exhibits impaired glycation.14 However, experimental protocols are neither well validated nor widely available. In this elderly woman, glycaemic control was guided by breakfast and rapid-acting insulin were given with breakfast and dinner. The dose of the long-acting glibenclamide was halved and small doses of short- and rapid-acting insulin were given with breakfast and dinner.

In conclusion, whereas general treatment guidelines recommend to aim for HbA1c values of 7.0% or lower, individual patient management demands targets to be tailor-made. Physicians should be aware of the fact that spuriously low HbA1c values can be caused by clinically silent haemoglobinopathies.

ACKNOWLEDGEMENT

Dr Brian Green, Waters Corporation, Altrincham, Cheshire, United Kingdom performed the α/β glycosylation ratios measurement.

REFERENCES

Disseminated intravascular coagulation and a negative D-dimer test

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ABSTRACT

The diagnosis of disseminated intravascular coagulation (DIC) requires the presence of a fibrin-related marker. D-dimer is frequently used in clinical practice as a fibrin-related marker. We present a case of paraneoplastic DIC with a false-negative D-dimer test. Repeating the test using a different D-dimer assay as well as the measurement of other fibrinolysis markers confirmed the diagnosis of DIC.

KEYWORDS

D-dimer, disseminated intravascular coagulation

BACKGROUND

Disseminated intravascular coagulation (DIC) is characterised by systemic activation of blood coagulation, which occurs under a variety of clinical conditions including sepsis, trauma, malignancy and obstetric disorders.1,2 The diagnosis of DIC suffers from the lack of a true gold standard. A scoring system for DIC in critically ill patients has been devised by the International Society of Thrombosis and Haemostasis (ISTH).2,3 This scoring system is based on an underlying disorder known to be associated with DIC, a diminished platelet count, a prolonged prothrombin time (PT), a low fibrinogen level, and the presence of a fibrin-related marker.2,3 Routinely, a D-dimer assay is used as a fibrin-related marker. Various D-dimer assays are commercially available. The selection of a D-dimer assay for the routine clinical practice is not only based on its performance, but also on its costs and efficacy.4,5 We report here a case in which a negative D-dimer test failed to initially confirm the diagnosis of DIC.
presence of fibrin degradation by another D-dimer assay (VIDAS, bioMerieux, France). This assay demonstrated a D-dimer value of 3.02 mg/l (normal <0.5 mg/l). In addition, antithrombin activity, plasminogen activity and α2-antiplasmin activity were decreased (table 1). With this, the diagnosis of paraneoplastic DIC was established. Because of the patient’s poor performance status, there were no therapeutic options for the metastatic disease and empirical treatment with tranexaminic acid was initiated.

**DISCUSSION**

The DIC score according to the recommendations of the ISTH includes a fibrin-related marker in order to differentiate DIC from other conditions associated with a lowered platelet count or prolonged clotting times. Fibrin is the product of fibrinogen interaction with thrombin, and its structure is stabilised by cross-linkage between the γ-chains catalysed by activated factor XIII. Intravascular formation of fibrin induces its concomitant proteolysis by plasmin, which results in degradation products with a wide range of molecular weights carrying various numbers of cross-linked D-domains, called D-dimers (figure 1). Applying the DIC score criteria to the presented case means that a normal D-dimer would result in 3 points (2 points for marked prolongation of prothrombin time, 1 point for lowered fibrinogen concentration). According to ISTH criteria, a score ≥5 points is compatible with the diagnosis of DIC. An elevated D-dimer would have correctly identified the diagnosis of DIC by increasing the score to 5 points. Currently, more than 30 D-dimer immunoassays based on more than 20 different D-dimer-specific antibodies are available, but an international standard is lacking. The performance of different D-dimer assays has been assessed predominantly in venous thromboembolic events (VTE), and varies due to differences in monoclonal antibodies, assay technology and calibration. The enzyme-linked immunosorbent assays (e.g. ELISA, VIDAS, bioMerieux) and the latex-based immunoassays (e.g. Tinaquant, Roche) are highly sensitive (>95%) with a high negative likelihood ratio for VTE at a cut-off value of 0.5 mg/l. The use of these D-dimer assays in routine clinical practice may be hampered by the long turnaround time or the specially required equipment. New rapid assays have been developed in order to increase the efficacy for the emergency situations. CARDIAC D-dimer assay (Roche)
uses whole blood instead of plasma and is measured on a reflectometer device producing a quantitative result in ten minutes. The performance of D-dimer assays for the diagnosis of DIC has not been so thoroughly evaluated. As many current D-dimer assays are optimised for exclusion of VTE, their measuring range may be too narrow for the diagnosis of DIC. In addition, the recommendations of the ISTH do not specify the fibrin-related marker. So for the diagnosis of DIC, fibrin/fibrinogen degradation products (FDPs) or soluble fibrin may be used as ‘fibrin-related markers’ too. More specialised tests measure the generation of thrombin and have a high sensitivity and specificity for DIC, but they are not generally available for the routine clinical practice.

The presence of DIC in severe illness has important therapeutic and prognostic implications. The management of DIC requires the treatment of the underlying disorder and supportive measures for the coagulopathy. Although in the presented case there were no therapeutic options, the management of other malignancies, such as acute promyelocytic leukaemia, benefits from rapid and reliable diagnosis of paraneoplastic DIC. Because D-dimer is routinely used as a fibrin-related marker, clinicians should be aware of the heterogeneity of the assays that measure D-dimer. Intensive collaboration between clinicians and clinical chemists is required when a clinical suspicion of DIC is not confirmed by a D-dimer test, because other fibrin-related marker tests may be employed.

**REFERENCES**

Chronic pancreatitis resulting from genetic mutations in trypsin and trypsin inhibitors

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Chronic pancreatitis (CP) is a rare condition characterised by progressive and irreversible inflammatory changes that potentially leads to exocrine and endocrine damage of the pancreas. Alcohol abuse is an important cause of CP, but other factors such as anatomical changes, metabolic disease and autoimmunity are also implicated. On the other hand, genetic factors clearly underlie a substantial portion of CP cases.1,2 The pace of developments in this field has been very rapid, making it appropriate to review some of the key advances. Trypsin and trypsin inhibitors are thought to be central to the pathogenesis of CP. Trypsinogen is produced in the pancreas, secreted into the small intestine, and converted to trypsin. Trypsin hydrolyses proteins into smaller peptides or amino acids. Premature pancreatic activation of trypsin and subsequent pancreatitis is the central concept in CP and documented by recent experimentation. The effect of genetics is most obvious in a familial form of pancreatitis. Here, CP is inherited in an autosomal dominant trait. Patients develop CP early, and the clinical profile is similar to that of non-inherited CP, but the lifetime risk for pancreatic cancer is very high. Mutations in cationic trypsinogen (PRSS1) cause familial CP. Two mutations, R122H and N29I, are very common and account for almost all familial cases assessed so far.3 Functional analysis of these mutants demonstrated enhanced autoactivation, pointing to a gain of function. This seems to support the concept that enhanced intrapancreatic trypsin causes pancreatic inflammation and autolysis. A second isoform of trypsinogen, anionic trypsinogen (PRSS2) is also involved in CP. A recent study showed that one PRSS2 mutant, G191R, actually protects against CP, as it was found in 3.4% of controls, but in 1.3% of affected individuals.4 It appeared that this mutant encoded non-functional trypsinogen, a severe loss of function. So far, disease enhancing PRSS2 mutants have not been found. The clinical implications are limited, though G191R carriers developed the disease at a significant later age.

One of the best-known trypsin inhibitors is serine protease inhibitor, Kazal type 1 (SPINK1). It appears that one specific mutation (N34S) is enriched in CP patients. Many case control studies show that N34S is found mostly in patients without a clear underlying cause for CP, as 15-40% of patients with so-called idiopathic CP carry N34S on one allele or on both alleles.5,6 Though it is logical to assume that N34S decreases the inhibitory effect of SPINK1, functional analysis does not show any effect. However, N34S is co-inherited with other, nearby located SPINK1 variants. It is conceivable that these variants cause the effect. The last, and most recent development is the discovery of trypsin-degrading enzyme chymotrypsin C (CTRC) variants. Similar to SPINK1 it inhibits trypsin and serves as a protective mechanism against pancreatitis. Using a very large European CP cohort it was shown that two CTRC mutants were significantly overrepresented in CP patients compared to controls (3.5 vs. 0.7%).7 Functional assays demonstrated that these mutants reduce CTRC activity and/or impair secretion. Again, the results accord with the common theme that loss of function of a trypsin inhibitory enzyme predisposes to CP, apparently by diminishing its protective trypsin degrading activity. All in all, these studies provide support for the central role of trypsin in the pathogenesis of CP. Without doubt future studies will identify other players in this pathway that modify the risk for CP.

REFERENCES

Letter to the Editor

Hydatid liver cyst ruptured into vena cava inferior

Dear sir,

I have read the paper entitled ‘Embolisation of hydatid cysts in the pulmonary artery presenting with haemoptysis’ and thank you for your study. I want to present a similar case and ask some questions.

A woman (32 years) with dyspnoea, cough and haemoptysis had an abdominal mass and the diagnosis of hydatid liver cyst was made by ultrasound. Computed tomography reported that the cyst was 12 x 8 cm in diameter, multiloculated and invading segments I, IV and VIII of the liver and possibly ruptured into the vena cava. MRI, Doppler ultrasound and cavagraphy confirmed cystic lesions in the retrohepatic vena cava and also in the pulmonary artery (figure 1). At first, treatment of the main hydatid focus in the liver was planned. Abdominal exploration demonstrated a hydatid liver cyst and because of the diagnosis of rupture into the inferior vena cava, the cyst was opened with caution after a control puncture with an angiocath. There was no blood in the cyst cavity, the cyst was opened and the membranes were removed. The inner surface of the cyst cavity was examined gently with a probe and during that meticulous examination a communication, 3 mm in a diameter, was found posterior to the vena cava. The communication was closed with sutures. We concluded that the higher intra-cystic pressure and the valvular functions of the pericystic folds prevented blood from the vena cava filling the cyst. An additional cystobiliary communication was sutured and the procedure was concluded with an omentopexy into the cyst. The postoperative course of liver surgery was uneventful and four months later she underwent surgery for pulmonary artery hydatid embolism. After pulmonary arteriotomy, a hydatid cyst, 5 x 5 cm in diameter, was removed and there was no need for pneumonectomy. After a follow-up of 18 months, she still had symptoms of chronic pulmonary embolism.

Hydatid pulmonary embolism from fistulisation or rupture of hydatid liver cysts is very rare. My questions are: What was the location, type and diameter of liver hydatid cyst? Was there any blood in the cyst cavity in the liver when it was opened. Is pneumonectomy necessary in those cases or is embolectomy alone enough. And, lastly, what was the primary focus (liver) in your patient when you operated the lung.

C. Kayaalp

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References

Ruptured hepatic cysts adjacent to the hepatic vein or the inferior vena cava may cause development of hydatid cysts either in pulmonary parenchyma or rarely pulmonary arteries.\textsuperscript{1,4} Our patient had a history of surgery for a hepatic hydatid cyst five years ago. Unfortunately, we did not have an opportunity to get a preoperative abdominal CT of the patient. However, a recently taken upper abdominal CT revealed that the patient most probably had multiple giant hepatic cysts neighbouring the inferior vena cava, because the lateral segment of the left liver lobe was totally resected, there was some calcification and residual cystic spaces were seen in the medial segment of the left liver lobe. Figure 1 demonstrates the calcified degenerative type V hydatid cyst in the primary focus. We had no information on whether there was any blood in the cyst cavity when it was opened.

Embolectomy and/or enucleation are generally accepted surgical procedures, especially for an isolated hydatid cyst, which is diagnosed early and causing proximal or distal pulmonary artery occlusion without any irreversible parenchymal or intimal arterial wall degeneration.\textsuperscript{1} Otherwise, lobectomy or pneumonectomy may be needed.\textsuperscript{1,5}

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A patient with a large periumbilical bruise and acute abdominal pain

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CASE REPORT

A 61-year-old male was admitted to the intensive care unit with acute respiratory insufficiency, hypotension and increasing abdominal pain. There was no known medical history and the patient was reported to drink about 10 units of alcohol daily. Physical examination showed an obese man in respiratory distress. He was afebrile with a blood pressure of 90/50 mmHg, pulse rate 100 beats/min regular and a respiratory rate of 30 breaths/min. His peripheral saturation was 90% breathing 12 litres oxygen through a non-rebreathing mask. Auscultation of the thorax and cardiac examination were unremarkable. Abdominal examination showed a periumbilical small bruise, which increased in size in the following days (figure 1). The abdomen was distended and tender on palpation without guarding.

WHAT IS YOUR DIAGNOSIS?

See page 406 for the answer to this photo quiz.
**Diagnosis**

Acute haemorrhagic pancreatitis was diagnosed based upon the reported alcohol consumption, clinical examination and the laboratory findings (total bilirubin 32 µmol/l, aspartate aminotransferase 136 U/l, alanine aminotransferase 85 U/l, and amylase 191U/l). The abdominal computerised tomography (CT) (figure 2) confirmed the diagnosis of pancreatitis and showed prominent peripancreatic inflammatory changes and extensive necrosis of more than 50% of the pancreatic parenchyma (CT severity index: score 9).

The skin discolouration in the periumbilical region is called Cullen's sign and reflects periumbilical grid cyanosis due to diffusion of retroperitoneal blood into the falciform ligament and, subsequently, to the subcutaneous umbilical tissues via the connective tissue covering the round ligament complex. Cullen first described the bluish periumbilical discoloration related to ruptured ectopic pregnancy. Cullen's sign is a well-known symptom of haemorrhagic pancreatitis although seldom observed. It is described in less than 3% of patients with an acute pancreatitis with an estimated mortality of 37%.

Four weeks after admission the patient died due to an uncontrollable intra-abdominal bleeding.

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**References**

PHOTO QUIZ

An unusual cause of rectal bleeding

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CASE REPORT

A 79-year-old man with acute onset of rectal bleeding was admitted to our hospital. There were no complaints of abdominal pain or nausea and he had previously been well without a history of recent illness or weight loss. On physical examination a solid palpable mass was found in the right lower quadrant of the abdomen. Digital rectal examination and colonoscopy were unremarkable, but colonoscopy did reveal blood coming from a proximal source. Subsequent gastroscopy was unremarkable. Therefore, an abdominal computed tomography scan with intravenous contrast was performed, which showed typical findings characteristic of the diagnosis (figure 1).

WHAT IS YOUR DIAGNOSIS?

See page 408 for the answer to this photo quiz.
DIAGNOSIS

The computed tomography (CT) scan shows a large, well-circumscribed heterogeneous mass in the left upper abdomen. Laparotomy was performed. The mass, with a diameter of 14 cm, originated from a Meckel’s diverticulum, and was causing the rectal bleeding (figure 2). The tumour was surgically removed and an end-to-end anastomosis was performed. Immunohistochemistry showed CD117 positive staining, being specific for a gastrointestinal stromal tumour (GIST).

Although the preoperative diagnosis of a complicated Meckel’s diverticulum is difficult, the diagnosis should be considered in case of an acute onset of rectal bleeding, especially when gastroscopic and colonoscopic examinations are unremarkable. The Meckel’s diverticulum is present in about 0.3 to 4% of the general population with a life-time complication rate of about 4%, decreasing with age. Neoplasms are rare and reported in approximately 0.5 to 3.2% of symptomatic Meckel’s diverticula.  

A CT scan with intravenous contrast (but no oral contrast administration) was the investigation of choice since the patient was haemodynamically stable. The site of potential blood loss is more readily detected since exposure to an adequate level of contrast lasts at least five times longer than during intra-arterial angiography. Moreover, a CT scan can yield an additional full anatomical overview of the patient. However, in an haemodynamically unstable patient, angiography is preferred because it provides the means for therapeutic embolisation.

REFERENCE

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