PHOTO QUIZ: Skin lesions as a first presentation, see page 264

Antithyroid drug regimens before and after $^{131}$I-therapy

IgA nephropathy

Cardiac complications after mediastinal irradiation

50 years Netherlands Journal of Medicine
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The mission of the journal is to serve the need of the internist to practise up-to-date medicine and to keep track with important issues in health care. With this purpose we publish editorials, original articles, reviews, controversies, consensus reports, papers on speciality training and medical education, book reviews and correspondence.

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SPECIAL REPORT
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Glomerular haematuria: not so benign?

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INTRODUCTION

Isolated haematuria is a frequent finding in routine clinical practice. In most cases haematuria is caused by glomerular disorders, in particular IgA nephropathy (23 to 75%), thin basement membrane nephropathy (5 to 35%), and non-IgA mesangiproliferative glomerulonephritis (9 to 24%).

Prognosis is considered to be good in these patients provided proteinuria, hypertension, and renal insufficiency are absent. Hence the term benign glomerular haematuria has been used to describe this condition. In many parts of Europe and the USA a renal biopsy is considered unnecessary in these patients, and they are referred to their general physician for life-long (bi)annual monitoring of serum creatinine concentration, proteinuria and blood pressure.

In this issue of the Netherlands Journal of Medicine, Shen et al. present their analysis of patients with clinically early IgA nephropathy, defined as biopsy-proven IgA nephropathy with haematuria and no or minimal proteinuria, normal blood pressure, and normal renal function. The authors show that after a mean follow-up of ten years progressive renal failure occurred in up to 24% of patients.

What lessons can be learned from these data and should we adopt a more vigorous renal biopsy policy?

HAEMATURIA IS A COMMON PROBLEM

In China and other Asian countries screening programmes are used to identify persons with minimal urinary abnormalities. Shen et al. report a prevalence of haematuria in the screened population of 8.5%. Similar prevalence rates have been reported for the European population, with a range of 0.8 to 16.1%. This wide range results from the variance in age and sex distribution of the populations studied and whether the diagnosis was based on dipstick test alone or also on microscopic examination of the urinary sediment.

IMPORTANT TO DIFFERENTIATE BETWEEN GLOMERULAR AND NONGLOMERULAR HAEMATURIA

Although microscopic haematuria is generally of glomerular origin, it is important to exclude urological causes. The latter is even more important in the elderly, where haematuria more often results from malignancies such as bladder carcinoma. Shen et al. performed urological investigations in all patients with haematuria to exclude urological causes. Of note, the authors do not mention the urinary sediment as an important tool to differentiate between glomerular and nonglomerular haematuria.

Glomerular haematuria is characterised by the presence of dysmorphic erythrocytes, whereas in urological diseases monomorphic erythrocytes are observed. Moreover, the presence of erythrocyte casts is virtually pathognomonic for glomerular haematuria.

In a study designed to evaluate the significance of dysmorphic erythrocytes in the urinary sediment for discrimination between urological and nephrological causes of haematuria, the percentage of dysmorphic erythrocytes was determined in urine samples of 107 patients with known glomerular or urological haematuria. When different thresholds for the number of dysmorphic erythrocytes were chosen, a percentage of dysmorphic erythrocytes of 40% or less had a sensitivity of 100% and a specificity of 67% to diagnose urological haematuria. In other words when using this threshold no urological causes of haematuria would be missed, although 33% of patients with glomerular haematuria would falsely be presumed to suffer from an urological disease and might therefore unnecessarily be subjected to urological investigations.

When the presence of erythrocyte casts was also considered a criterion for nephrological pathology, the specificity to diagnose urological pathology rose to 88.1% while sensitivity remained 100%. Importantly, when urinary sediment is not performed as initial diagnostic procedure in the evaluation of haematuria, the number of patients who are unnecessarily exposed to urological examinations will be much higher.
Thus, a thorough investigation of the urinary sediment by an experienced technician or physician according to strict criteria is a reliable aid in determining the optimal strategy to be followed in patients with haematuria. Adopting an approach for the evaluation of haematuria which includes initial screening of the urinary sediment prevents many unnecessary, expensive and often invasive urological tests.

**Proteinuria, Not Haematuria, Determines Renal Outcome**

Shen et al. observed that 24% of patients developed renal insufficiency (defined as estimated GFR <60 ml/min/1.73 m²) during follow-up. Similar results were reported by Szeto et al. who studied a cohort of 72 patients with IgA nephropathy, haematuria and minimal proteinuria. After a median follow-up period of seven years, more than 40% of the patients had evidence of progressive renal injury as determined by proteinuria (33%), hypertension (26%) or impaired renal function (7%). Other studies have also shown that haematuria is an independent risk factor for the development of chronic kidney disease. Taken together, these data suggest that patients with glomerular haematuria have a less favourable prognosis. Thus, haematuria might not be so benign after all.

When the data are scrutinised in more detail, it appears that patients with persistently isolated haematuria do not develop renal insufficiency. In fact, it is proteinuria that counts. In the study by Shen et al. progressive renal failure only occurred in patients who had proteinuria at baseline or developed proteinuria during follow-up. Similar observations were made by other investigators studying the prognosis of patients with asymptomatic haematuria. In these studies, approximately 10% of the patients developed proteinuria during the follow-up period. While 10 to 15% of the patients with proteinuria subsequently developed renal insufficiency, none of the patients with persistent isolated haematuria exhibited a decline of renal function. Thus, impairment of renal function only occurred in patients who had developed proteinuria and often also hypertension. Consequently, a renal biopsy will not aid in the management of patients with haematuria with no or only slight proteinuria. Current practice consisting of life-long follow-up with monitoring of blood pressure and proteinuria at regular intervals will allow timely identification of those patients with haematuria at risk for progression to renal insufficiency. Postponing a renal biopsy until proteinuria becomes evident is therefore justified, particularly since renal biopsy is an invasive procedure with a small but significant risk of complications.

In the study by Shen et al. most patients with progression (91%) developed proteinuria >1 g/day. Of note, this level of proteinuria was also the threshold for progression in a recent study by Reich et al. These authors reported the clinical course in 542 patients with IgA nephropathy. Patients received variable treatment regimens. It appeared that if proteinuria was lowered to values below 1 g/day no progression occurred.

**Prednisone Treatment May Be Effective**

Reduction of proteinuria is the mainstay of treatment in patients with IgA nephropathy. It is evident that the natural history of IgA nephropathy can indeed be modified by therapeutic interventions with either ACE inhibitors, angiotensin II-receptor blockers (ARBs), or the combination of these drugs. Kobayashi et al. have pointed to the benefits of steroid therapy in patients with IgA nephropathy. The best rationale for corticosteroids in patients with IgA is derived from a randomised controlled trial in patients with a glomerular filtration rate greater than 70 ml/min and proteinuria between 1 to 3.5 g/day. Patients were assigned randomly to supportive therapy only or additional corticosteroids. After ten-year follow-up, serum creatinine levels had doubled in one of 43 patients in the steroid group vs 13 of 43 in the control group (p<0.01). After one year, in 11 (26%) of the treated patients proteinuria had decreased below 0.5 g/day. Whether these results can be generalised has been questioned since in the study by Pozzi et al. only six patients in each group were treated with ACE inhibitors. Shen et al. add some useful information. They treated all patients with proteinuria with ACE inhibitors and/or ARBs. If despite this treatment proteinuria exceeded the level of 1 g/day additional prednisone therapy was advised. Overall, 52 of 177 patients received prednisone. The majority of patients responded to prednisone and no less than 66% of the prednisone-treated patients achieved a complete remission defined as proteinuria below 0.15 g/day. Thus, also in patients on ACE inhibitor treatment prednisone may be effective.

**Conclusion**

IgA nephropathy is a common cause of isolated microscopic haematuria. The clinical course of patients with IgA nephropathy and isolated haematuria is quite variable, and up to 20% of patients will progress to ESRD in 20 years. A policy of biopsying all such patients is not without risk and does not influence therapy. All patients need to be carefully followed for the development of proteinuria and/
or hypertension as signs of future progression. Obviously, many patients will be followed unnecessarily. Ideally, in the near future, it should be possible to identify those patients who are at risk for progression with a noninvasive test using more sophisticated biomarkers.

REFERENCES


We present a 62-year-old man who over the years developed almost all the possible cardiac complications of radiation therapy after treatment of a Hodgkin's lymphoma. A review of the literature and a summary of treatment options for cardiac complications after irradiation of the mediastinum for Hodgkin's lymphoma are presented.

**Keywords**
Cardiac complications, Hodgkin's lymphoma, irradiation

**Case Report**
A 62-year-old male patient was admitted to our hospital for planned re-re-coronary artery bypass grafting (CABG), as well as mitral and aortic valve replacement.

In 1974, a large mass in the patient's right cervical region and a collection of smaller lymph nodes in the left cervical region were discovered. A biopsy of the mass in the right cervical region was taken. Histological examination showed Hodgkin's lymphoma (HL) of mixed cellularity subtype. Neither involvement of any other lymph node region on either side of the diaphragm, nor involvement of the spleen or of any extralymphatic organ was discovered. The patient was classified as stadium IIA.

The lymphoma was primarily treated with mantle field irradiation (exact dose and duration of treatment unknown), involving the right and left cervical regions, both armpit regions and the mediastinum. In addition, the para-aortic lymph nodes and the spleen were irradiated. After initial irradiation therapy, the patient was treated with vinblastine sulphate injections for two years in the setting of a clinical trial. Treatment was completed after 2.5 years and the patient was declared to be in total remission.

In April 2006 the patient presented with complaints of progressive dyspnoea, oedema and weight gain. He had never smoked, nor did he have any other risk factors for cardiovascular disease. On physical examination a rough systolic murmur III/VI over the aortic valve, the apex and the carotid area was heard; auscultation of both lungs revealed fine rales. Pretibial oedema was present. The chest X-ray showed an increased heart-thorax ratio and transoesophageal echocardiography (TEE) revealed a moderate decrease in left ventricular function, thickening...

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
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<tbody>
<tr>
<td>1974</td>
<td>Hodgkin's disease stadium IIA Mantle field irradiation Irradiation of para-aortic lymph nodes and spleen Vinblastine sulphate therapy</td>
</tr>
<tr>
<td>1976</td>
<td>Total remission</td>
</tr>
<tr>
<td>1993</td>
<td>Unstable angina pectoris Coronary angiography: right-sided one-vessel disease Therapy: CABG (AO-RPL-RPD)</td>
</tr>
<tr>
<td>1998</td>
<td>Sick sinus syndrome Therapy: DDD-R pacemaker</td>
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<tr>
<td>2003</td>
<td>Transient ischaemic attack of the brain</td>
</tr>
<tr>
<td>2005</td>
<td>Revision of pacemaker system to bi-ventricular pacemaker with one electrode in the right ventricle-outflow tract Admitted to hospital three times with signs and symptoms of right- and left-sided heart failure</td>
</tr>
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CABG = coronary artery bypass grafting; TEE = trans-oesophageal echocardiography.
of the mitral valve with grade 2 mitral valve regurgitation resulting from dilatation of the valve ring and severe calcifications of the aortic valve with an aortic valve area of 0.6 cm². Coronary angiography showed a 60% stenosis of the main stem of the left coronary artery (LCA) and severe proximal calcifications of the left anterior descending artery (LAD). The right coronary system showed several sites of severe stenosis of the grafts. Although aortic valve replacement was indicated this would mean a third, high-risk operation on a patient with previous radiation therapy of the mediastinum, and the intervention was therefore postponed whilst conservative therapy was intensified.

Progressive dyspnoea and four episodes of collapse of cardiac origin led to readmission. Atrial fibrillation secondary to severe right- and left-sided cardiac failure with dilatation of both sides of the heart was diagnosed. At this point surgery to undergo re-re-CABG, aortic and mitral valve replacement was considered inevitable to improve the patient’s condition. The intervention was complicated because of a constrictive pericarditis, showing multiple sites of calcifications and adherence of previously constructed venous grafts. A new grafting procedure was therefore technically impossible. The aortic and mitral valves were replaced and an intra-aortic balloon pump was inserted.

The postoperative period was complicated by acute renal failure for which continuous veno-venous haemodiafiltration (CVVH) was started. During treatment on the ICU the patient developed pneumonia with *Streptococcus pneumoniae* and *Pseudomonas* bacteria. In spite of circulatory support with inotropic agents and treatment of the infectious complications, the patient developed a refractory cardiogenic shock and multiple organ failure. The patient died as a result of this condition.

Histopathology of both the aortic and mitral valves showed fibroid and mucoid degenerative changes and calcifications with sites of chronic infiltrations secondary to these changes.

**DISCUSSION**

Cardiovascular complications after treatment for Hodgkin’s lymphoma can arise due to both radiation therapy and chemotherapy.

Cardiotoxicity following chemotherapy is mainly associated with the use of anthracyclines. This drug causes direct damage to the myoepithelium and cardiotoxicity is strongly associated with the cumulative dose. From the use of vinblastine sulphate alone, no direct toxic effects on the heart have been described.

Radiation injury may develop acutely or over the course of several years after exposure and typically leads to progressive tissue fibrosis, necrosis, atrophy and vascular damage. The spectrum of mediastinal injury is wide, ranging from minor fibrosis to heavy scarring and fusion of mediastinal structures with extensive cardiac and great vessel disease. Radiation-induced cardiac damage is the next most frequent cause of treatment-related morbidity after second malignancies in HL and accounts for 25% of mortality in cured patients. Cardiovascular complications depend upon the total radiation dose, the percentage of the heart that is being irradiated and the fractionation scheme, dose per fraction and field size. Aleman et al. studied the primary cause of death of patients who had been treated for HL before the age of 41, between 1965 and 1987. Increased absolute and relative risks (RRs) of death resulting from cardiovascular disease and myocardial infarction were found. The RRs were especially increased in patients treated before the age of 21. Consistent with other studies, a declining trend of these specific RRs was observed with advancing age. This may be due to the strong increase in baseline risk for cardiovascular disease and myocardial infarction with advancing age in the general population.

This same group studied the risk factors for cardiovascular disease in patients who were treated for HL and who survived at least five years after treatment. Compared with the general population, the incidence of valvular disease, myocardial infarction and congestive heart failure was shown to be three- to five-fold increased after treatment for HL. Mediastinal radiotherapy is associated with a significant two- to seven-fold increase in the risk of myocardial infarction, angina pectoris, congestive heart failure and valvular disorders.

Cardiovascular risk factors in general, such as hypertension, hyperlipidaemia, obesity, diabetes mellitus, (history of) smoking and a positive family history may contribute to the risk of developing cardiac complications. Also, cardiovascular complications can occur indirectly, as irradiation of the renal region whilst treating para-aortic nodes and spleen can cause hypertension.

In the following section the cardiac complications after radiation therapy will be discussed in more detail.

**Pericarditis**

Approximately 20 to 40% of patients who have received mediastinal radiation therapy develop pericarditis; the incidence is proportional to dose and treatment volume. Acute radiation pericarditis usually develops a few weeks after treatment; chronic pericarditis can occur five to ten years after treatment even if the patient did not suffer from acute pericarditis. The pericardium becomes thickened as a result of fibroid changes; the vasculature within the pericardium shows characteristic changes leading to increased vascular permeability. Constrictive pericarditis has been reported...
to be a marker for greater radiation injury to the heart and is associated with ventricular diastolic dysfunction and high mortality.

Pericarditis is treated with nonsteroidal anti-inflammatory agents and drainage of the pericardial effusion if the patient is severely compromised. For recurrent symptomatic pericardial effusion, pericardial fenestration or pericardiectomy may be indicated. In case of constrictive pericarditis, pericardiectomy seems to be an effective form of therapy.\(^{11,12}\)

**Arrhythmias**

A wide variety of arrhythmias either as a result of direct damage to the cardiac conduction system or as a result of dysfunction of the autonomic regulatory functions after chest irradiation have been described: QT-interval prolongation, sick sinus syndrome, all grades of heart block, and loss of circadian and respiratory phasic heart rhythms.\(^{1}\) Crestanello et al. reported a prevalence of 27% of patients requiring a pacemaker as a result of damage to the conduction system after irradiation of the mediastinum.\(^{5}\)

**Coronary vasculature**

Cardiovascular calcification is a strong marker of the presence of atherosclerosis and occurs in patients after mediastinal radiotherapy for HL at a relatively young age. Coronary artery disease occurs almost exclusively in patients with other cardiac risk factors.\(^{9}\) A prevalence of 53% of patients with coronary artery disease after mediastinal irradiation has been reported.\(^{2}\)

Osteal stenosis is typical for radiation-induced coronary artery disease. Subtle differences from common atherosclerosis are typical for radiation-induced atherosclerosis: subintimal fibrosis, proliferation and paucity of lipid in the atherosclerotic plaque.\(^{8,10}\)

Usually the right coronary and left anterior descending coronary arteries are included in a common mantle radiation field, typically resulting in stenosis of these vessels. Percutaneous transluminal coronary angioplasty alone appears to have a high rate of restenosis.\(^{8}\) Surgical arterial revascularisation using one or both internal thoracic arteries has good long-term results.\(^{11}\)

In a retrospective analysis, early and late results of coronary artery bypass grafting for the treatment of ischaemic heart disease after mediastinal radiation therapy were studied. The mean interval between mediastinal radiation therapy and CABG was approximately 15 years. A substantial number of the included patients needed concomitant valve surgery. Early results such as operative mortality, sternal wound infection, and one to five year survival were good. Late survival was limited by malignancy, recurrent or new, and by the development of valvular disease (30%) and heart failure. No cases of re-CABG were mentioned in this study.\(^{12}\)

**Noncoronary atherosclerotic vascular disease**

The overall estimated incidence of noncoronary atherosclerotic vascular disease in HL survivors after radiation therapy is 7.4%, including carotid artery stenosis and subclavian artery stenosis. Aortic calcification secondary to atherosclerotic changes typically occurs in patients over 60 years of age, and is characteristically present in the aortic arch. In various studies, aortic calcification after irradiation of the mediastinum has been described to occur typically in the ascending aorta, as this site is probably more vulnerable to radiation injury due to its location more anteriorly than the aortic arch.\(^{23}\)

**Valvular dysfunction**

Cardiac valve disease develops in approximately 60% of patients with previous radiation therapy of the mediastinum and is an important source of long-term morbidity among HL survivors. This condition is progressive, with clinically important valvular dysfunction increasing with time after radiation and being more severe when radiation has taken place at a younger age. Most patients are asymptomatic with valve regurgitation being more prevalent than valve stenosis. Fibrosis and calcification are typical changes of the cardiac valves that have been reported after radiation therapy, often with progression to heart failure and death.\(^{5,9,10}\)

Left-sided valvular radiation disease is predominant.\(^{4}\) Heidenreich et al. reported that abnormalities of the aortic valve were more common than abnormalities of the mitral and tricuspid valves after irradiation of the mediastinum. The increased incidence of aortic valve involvement is most probably the result of its location nearer to the mediastinal radiation field than the other valves mentioned.\(^{7}\)

In patients with cardiac valve disease and no previous radiation therapy of the mediastinum, preservation of the native valve by surgical repair is associated with better outcome in long-term survival, preservation of ventricular function, and freedom from reoperation, thromboembolism and anticoagulant-associated morbidity. Crestanello et al. were the first to examine whether these advantages of valve repair were also present in patients with radiation-associated mitral and tricuspid valve disease. They studied 22 patients who had mitral or tricuspid valve repair from 1976 to 2001. Early results at five years after operation showed overall survival of 66%, freedom from cardiac death and from valve reoperation or cardiac valve transplantation of 85 and 88% respectively.

Durability of valve repair in long-term survivors was limited as severe dysfunction of the repaired valve developed in one third of the patients, resulting in reoperation in 16%. Progression of coronary artery disease and myocardial and valve fibrosis may contribute to progressive deterioration of cardiac valve function, irrespective of a successful initial

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Radiation-induced injury of the heart develops over the diaphragm, oesophagus and the heart and great vessels of the mediastinum, such as the chest wall, pleura, and lung, damage to all the different anatomic structures of the mediastinum. Mediastinal irradiation for Hodgkin’s disease can cause cardiac injury represented.

In our patient almost all the possible cardiac complications after radiation therapy of the mediastinum are from a new second malignancy and recurrence of the original disease as well. 15

Heart failure was reported in a study done by Handa et al. Heart transplantation for radiation-induced end-stage heart failure such as ischaemic and valvular heart disease after irradiation was 14%. The authors showed that patients with diastolic dysfunction had decreased cardiac event-free survival and were more likely to have stress-induced ischaemia than patients with normal diastolic function. 13

Both systolic and diastolic dysfunction may partially be explained by an increase in myocardial fibrosis after irradiation, but also by other factors contributing to cardiac failure such as ischaemic and valvular heart disease after irradiation of the mediastinum.

Heart transplantation for radiation-induced end-stage heart failure was reported in a study done by Handa et al. in 2000. The early results of this study were positive with all four patients surviving 48 months after transplantation. At that time all the patients were free from a new second malignancy and recurrence of the original disease as well. 15

CONCLUSION

In our patient almost all the possible cardiac complications after radiation therapy of the mediastinum are represented.

Mediastinal irradiation for Hodgkin’s disease can cause damage to all the different anatomic structures of the mediastinum, such as the chest wall, pleura, and lung, diaphragm, oesophagus and the heart and great vessels. Radiation-induced injury of the heart develops over the course of years and is usually more severe with high mediastinal doses (total dose and dose per fraction), minimal protective cardiac blocking and when radiation is given at younger age. The attending physician should be aware of the possible acute and late cardiac complications of treatment for HL and distinguish them from cardiac disease with another underlying mechanism. Treatment should be tailored towards the experience given in the medical literature.

REFERENCES

Antithyroid drug regimens before and after $^{131}$I-therapy for hyperthyroidism: evidence-based?

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ABSTRACT

Background: In view of the new national guideline on thyroid dysfunction, the evidence base for current practice as well as the new guideline is assessed with regard to the use of antithyroid drugs (ATDs) before and after radioiodine ($^{131}$I) therapy.

Methods: In December 2006, we surveyed 16 hospitals by telephone about different aspects of their antithyroid drug regimen: all eight academic centres and eight nonacademic teaching hospitals. The literature was searched for an evidence-based answer to each question in the inquiry.

Results: 13 of 16 hospitals (81%) use antithyroid drugs for pretreatment before $^{131}$I. ATDs are discontinued on average four days before $^{131}$I or diagnostic scan. However, 27% stop only three days beforehand, which may diminish the effect of $^{131}$I. Propylthiouracil (PTU) is also withdrawn four days before $^{131}$I, although the literature shows that PTU diminishes the effect of $^{131}$I even if it is stopped 15 days beforehand. Resumption of ATDs after $^{131}$I to prevent thyrotoxicosis is common practice (81%). One hospital (6%) never restarts ATDs, two (13%) only by indication. Adjunctive treatment consists of combination therapy in 93%, is usually resumed within two days after $^{131}$I therapy, and then continued for two to six months. Routine adjunctive treatment is not evidence-based and may be limited to a high-risk subset, especially elderly patients (>70 years) and patients with cardiac comorbidity. Resumption of ATDs within five to seven days after $^{131}$I may diminish the effect of $^{131}$I.

Conclusion: Antithyroid drug regimens in the Netherlands are heterogeneous. The evidence base of current practice and the new guideline are discussed.

KEYWORDS

Antithyroid drugs, hyperthyroidism, radioiodine therapy

BACKGROUND

In the Netherlands, Graves' hyperthyroidism is initially treated with antithyroid drugs (ATDs). In case of recurrence, radioactive iodine ($^{131}$I) is usually the preferred definitive treatment. ATDs are often used before and after treatment with $^{131}$I for prevention of symptomatic hyperthyroidism. ATDs are withdrawn a few days before $^{131}$I therapy, because continuous use during $^{131}$I therapy diminishes radioiodine uptake into the thyroid gland by blocking the organification of iodine. This results in a substantial (up to 50%) reduction of the final cure rate, defined as hypothyroidism or euthyroidism 12 months after $^{131}$I therapy, based on fixed doses of radioiodine.13 In most hospitals, resumption of ATDs following $^{131}$I therapy is common practice. Usually patients are treated for a period of two to three months after $^{131}$I, because it can take six to eight weeks before the effect of $^{131}$I becomes noticeable.

Between hospitals, ATD regimens appear to differ substantially, especially regarding the application of pretreatment, the withdrawal period before $^{131}$I therapy, resumption after $^{131}$I therapy and the time frame of the adjunctive treatment. The issue of a national guideline for treatment of hyperthyroidism, as well as the anticipated heterogeneity in ATD regimes used in the Netherlands, were reasons to audit the current practice. Our purpose is to compare current practice with the new guideline with regard to the use of antithyroid drugs before and after $^{131}$I, and to examine to what extent both practice and guideline are evidence-based.

MATERIALS AND METHODS

In December 2006, we surveyed 16 hospitals by telephone: all eight academic centres as well as eight nonacademic...
teaching hospitals, each corresponding to a different academic region. The Chief of the Endocrinology Department was asked to answer the following questions:

1. Do you use antithyroid drugs for pretreatment before or as adjunctive treatment after \(^{131}\)I therapy for hyperthyroidism?
2. Which antithyroid drug do you prefer?
3. How long before \(^{131}\)I therapy is methimazole withdrawn?
4. If propylthiouracil (PTU) is used, how long before \(^{131}\)I therapy is it withdrawn?
5. How long before \(^{131}\)I therapy is levothyroxine withdrawn?
6. Are antithyroid drugs resumed after \(^{131}\)I treatment? If yes, when? With or without levothyroxine? What is the time frame of the adjunctive treatment?
7. Does your hospital have its own guideline on this subject?
8. Are you in need of an evidence-based national guideline?

We made use of a standardised questionnaire, which was filled in for each telephone call.

In addition, the literature was searched for evidence-based answers to each question in the inquiry. PubMed was searched using the sensitive search strategy ((methimazole OR thiamazole OR carbimazole OR propylthiouracil OR antithyroid drug*) AND (radioiodine therapy OR radioactive iodine) AND (hyperthyroidism OR hyperthyroidism[mh])) which was limited by the therapy filter in ‘clinical queries’ and restricted to human and English. Reference lists of the identified studies were hand-searched for relevant publications. The retrieved articles were assessed for quality, resulting in levels of evidence and grades of recommendation.

RESULTS

Results of the inquiry

In 13 of 16 hospitals (81%) pretreatment with ATDs before \(^{131}\)I therapy is common practice. The ATD is discontinued three to 14 days before \(^{131}\)I or diagnostic scan (average 4 to 5 days), but 27% stop three days before \(^{131}\)I. Two hospitals (13%) use a withdrawal period longer than five days. There appear to be large differences between hospitals with regard to the withdrawal period of levothyroxine (from 3 days to 6 weeks, 77% stop less than four weeks before \(^{131}\)I). One hospital does not stop levothyroxine at all before \(^{131}\)I. The withdrawal period used for PTU does not differ from thiamazole. Resumption of ATDs after \(^{131}\)I therapy is standard practice in 13 hospitals (81%). One hospital (6%) never restarts ATDs, two (13%) only by indication. Adjunctive treatment after \(^{131}\)I consists of combination therapy in 93% and is usually resumed within two days after \(^{131}\)I therapy. Thereafter, ATDs are continued for six weeks to six months (very variable, on average four months). Eight hospitals (50%) do not have their own guideline on this subject. Twelve of 16 hospitals (75%) are in need of a national, evidence-based guideline.

Results of literature study

The extensive search in PubMed yielded 22 relevant articles. Four studies examined the influence of the withdrawal period of ATDs on the final outcome of \(^{131}\)I therapy.\(^{4-7}\) Examined withdrawal periods were 1, 4, 6 and 16 days. Only the studies assessing withdrawal periods of 4, 6 and 16 days before \(^{131}\)I were of sufficient methodological quality. Results show that a withdrawal period of four days is as good as no pretreatment, with regard to the final outcome of \(^{131}\)I. Another study, showing that a withdrawal period of three days is long enough to provide sufficient radiiodine uptake into the thyroid, was not taken into account because the final outcome of \(^{131}\)I was not a study endpoint.\(^{8}\) A recent meta-analysis suggests that antithyroid drugs increase failure rates of \(^{131}\)I when given in the week before or after \(^{131}\)I therapy, but no firm conclusions are drawn regarding the optimal interruption period of ATDs.\(^{9}\) Based on the available literature, we conclude that ATDs should be discontinued at least four days prior to \(^{131}\)I, otherwise the cure rate of \(^{131}\)I will be reduced.\(^{9}\) Dose regimens adapted to uptake rather than fixed doses of radiiodine may compensate for this effect. Five studies show that pretreatment with PTU is associated with a significant increase in the failure rate of \(^{131}\)I therapy, even if the drug is discontinued four to 15 days before \(^{131}\)I.\(^{10-14}\) The failure rate one year after a single dose of radiiodine is twofold when PTU is discontinued four to seven days before \(^{131}\)I, compared with no pretreatment or pretreatment with another antithyroid agent. A possible explanation may be that much higher doses of PTU are needed to achieve euthyroidism, resulting in larger radioprotective effects of PTU compared with thiamazole.

However, thus far methimazole and PTU have never been compared head-to-head in a randomised clinical trial. Little evidence is available on the withdrawal period of levothyroxine. Studies examining the effect of continuous use of levothyroxine during \(^{131}\)I therapy on the final cure rate are lacking. For patients it would be much easier if both thiamazole and levothyroxine could be stopped simultaneously. In toxic nodular goitre or toxic adenoma, stopping levothyroxine could even be harmful as this may lead to uptake of \(^{131}\)I in and radiation of healthy parts of the thyroid.

In most hospitals, resumption of ATDs following \(^{131}\)I therapy is common practice. Usually patients are treated for a period of two to three months after \(^{131}\)I, because it can take six to eight weeks before the effect of \(^{131}\)I becomes noticeable. Arguments in favour of this practice include prevention and treatment of symptomatic hyperthyroidism and thyrotoxicosis due to ATD withdrawal or radiation thyroiditis. The question arises if this is really necessary.
A small study shows that short-term increases in thyroid hormone levels occur primarily as a result of discontinuing antithyroid therapy rather than treatment with $^{131}I$ itself. These results have been proved by two randomised controlled trials. The mean increase in free thyroxine (FT4) levels after discontinuation of antithyroid therapy is 50 to 86%. Higher levels of thyroid-stimulating hormone (TSH) receptor autoantibodies at diagnosis are associated with increased worsening of thyrotoxicosis after stopping ATD treatment. Free T4 levels peak seven to 14 days after $^{131}I$ therapy, after which the levels gradually decrease. Patients who are not pretreated do not experience an increase, but a 32% decrease in FT4 levels during the first two weeks after iodine treatment. Free T4 levels stabilise during the first 30 days after $^{131}I$ therapy. This period can be well bridged by a resumption period of three or four days are lacking, early five days may also be safe. Because studies examining a resumption period of three months after $^{131}I$ for Graves’ hyperthyroidism are very heterogeneous. The design of a small study shows that ATDs reduce therapeutic efficacy of $^{131}I$ by their radioprotective properties (inhibition of the production of hydrogen peroxide), which may hamper the intended cytogenetic damage induced by the $^{131}I$ radiation. When ATDs can be resumed after $^{131}I$ remains a matter of debate. It is not possible to draw firm conclusions based on the literature. The only randomised study on this subject shows that resumption of methimazole seven days after $^{131}I$ therapy prevents the early and transient thyrotoxic phase, without interfering with the ultimate therapeutic efficacy of the $^{131}I$ treatment. Resumption after five days may also be safe. Because studies examining a resumption period of three or four days are lacking, early resumption of ATDs within five days after $^{131}I$ therapy should not be recommended as this may diminish the effect of $^{131}I$.

**DISCUSSION**

How evidence-based is the new guideline? Our study shows that ATD regimens before and after $^{131}I$ for Graves’ hyperthyroidism are very heterogeneous. The design of the inquiry may have limitations and it is obvious that we restricted our survey to endocrinologists. The results of the inquiry suggest that the new guideline on Thyroid Dysfunction will fulfil an important need. We hope that the guideline also contributes to more uniformity with regard to the use of ATDs around $^{131}I$ therapy. The guideline pays attention to this subject in chapter II.3.3 (pages 28-29) with the following recommendations: 1) Methimazole is preferred to PTU as pretreatment before $^{131}I$. If PTU is used, this should be withdrawn ten days before $^{131}I$ treatment. 2) Methimazole (and levothyroxine) should be stopped from three days before to three days after $^{131}I$ therapy. 3) Adjunctive treatment with ATDs is advised for a period of three months after $^{131}I$.

The message that PTU should be avoided as much as possible as pretreatment before $^{131}I$ and, if used, should be stopped longer before $^{131}I$ therapy than methimazole is important because current compliance to this relatively new evidence is poor. However, it is a matter of debate whether ten days is enough. Two studies show that the cure rate was still significantly reduced when PTU was discontinued 15 to 35 days before $^{131}I$ therapy. Based on the available literature, our advice would be to stop PTU at least two weeks before $^{131}I$ treatment.

With regard to withdrawal of methimazole before $^{131}I$, only a period of four days can be currently supported by good quality evidence. A withdrawal period of three days is advised in the new guideline. At the moment, it is not proven that a withdrawal period of only three days does not diminish the effect of the $^{131}I$ therapy (without increasing the radiiodine dose). However, evidence that a three-day period is inferior to a four-day period is also lacking.

Evidence from two studies shows that resumption of ATDs seven days after $^{131}I$ does not reduce the therapeutic efficacy of $^{131}I$; however a period shorter than five days may diminish the ultimate cure rate. A recent meta-analysis of RCTs shows that use of ATDs in the week before and after $^{131}I$ is associated with an increased risk of treatment failure. Furthermore, the benefit of routine adjunctive treatment for a period of three months after $^{131}I$, which is common practice in the Netherlands, can be questioned. From a theoretical and practical point of view, this policy is effective for prevention of symptomatic hyperthyroidism. However, evidence from two randomised controlled trials suggests that ATDs after $^{131}I$ have little additional value. The increase in FT4 occurs primarily as a result of discontinuing antithyroid therapy rather than $^{131}I$ therapy and peaks within seven to 14 days. The incidence of exaggerated hyperthyroidism including thyroid storm after $^{131}I$ is only 0.3%. The incidence of new onset atrial fibrillation after $^{131}I$ is 0.2% with and 0.5% without ATDs. The number needed-to-treat for prevention of thyroid storm or atrial fibrillation would be 333. Instead of routine application of ATDs after $^{131}I$, one may consider limiting adjunctive treatment to a subset of patients with a high risk of thyrotoxicosis with clinical implications, especially elderly patients.
patients (>70 years) and patients with cardiac comorbidity. This would be a safe and cost-effective alternative, as most patients can be treated with a β-blocker only. An overview of our recommendations is shown in table 1.

<table>
<thead>
<tr>
<th>Grades</th>
<th>Recommendations</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A</td>
<td>Antithyroid drugs should be withdrawn at least 4 days before 131I therapy in order to prevent treatment failure</td>
<td>5-7</td>
</tr>
<tr>
<td>Grade B</td>
<td>Pretreatment with propylthiouracil (PTU) diminishes the effectiveness of 131I treatment, even if it is stopped 4 to 15 days before. If used, PTU should be stopped at least 2 weeks before 131I therapy</td>
<td>10, 11, 13, 14</td>
</tr>
<tr>
<td>Grade A</td>
<td>Routine adjunctive treatment with antithyroid drugs for prevention of symptomatic hyperthyroidism is not evidence-based</td>
<td>15-17</td>
</tr>
<tr>
<td>Grade A</td>
<td>Antithyroid drugs should not be restarted sooner than 7 days after 131I therapy</td>
<td>9, 20, 22</td>
</tr>
<tr>
<td>Grade D</td>
<td>Resumption within 7 days may weaken the effect of 131I due to antioxidative properties and a decrease in thyroid metabolism</td>
<td>19</td>
</tr>
</tbody>
</table>

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We thank the following hospitals for their contribution to the inquiry: Academic Medical Center, Onze Lieve Vrouwe Gasthuis, VU Medical Center, Amsterdam; Medical Centre Alkmaar; University Medical Center Groningen; Medical Centre Leeuwarden; Leiden University Medical Center; Haga Hospital location Leyenburg, Den Haag; Maastricht University Hospital; Catharina Hospital, Eindhoven; Radboud University Nijmegen Medical Centre; Rijnstate Hospital, Arnhem; Erasmus MC location Dijkzigt, Rotterdam; University Medical Center Utrecht; Diakonessenhuis Utrecht.

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10. Tuttle RM, Patience T, Buss T. Treatment with propylthiouracil before radioactive iodine therapy is associated with a higher treatment failure rate than therapy with radioactive iodine alone in Graves' disease. Thyroid 1995;5:437.

Clinical course and prognostic factors of clinically early IgA nephropathy

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ABSTRACT

Background: Immunoglobulin A nephropathy (IgAN) is prevalent in many countries including China. At the time of diagnosis many IgAN patients present with normal renal function, proteinuria of 0.4 g/d or less, and normal blood pressure and they are classified as clinically early IgAN patients. However, the natural history of clinically early IgAN and prognostic factors has not yet been clarified.

Methods: We investigated 177 early IgAN patients (108 males and 69 females) followed up for a mean period of 111 ± 43 months.

Results: During the follow-up period among 177 clinically early IgAN patients, urinary abnormalities disappeared in 9% of the patients; increased proteinuria was present in 79 patients (46%). The prevalence of hypertension was 38% (68 patients), and 24% (43 patients) developed renal insufficiency. Poor renal outcome was associated with haematuria, urinary protein excretion index (UPEI, the product of urinary protein excretion at the time of renal biopsy and prebiopsy duration), and tubulointerstitial lesions.

Conclusion: Renal outcome is dismal in patients with clinically early IgAN. Haematuria, UPEI, and tubulointerstitial lesions could be useful markers of a progressive course.

KEYWORDS

IgA nephropathy, histological lesion, proteinuria, renal progression

BACKGROUND

Primary immunoglobulin A nephropathy (IgAN) is the most prevalent glomerular disease throughout the world. At the time of diagnosis many patients with IgAN present with normal renal function, a proteinuria of 0.4 g/d or less, and normal blood pressure, and these patients are classified as clinically early IgAN patients. In the absence of progressive factors such as renal insufficiency, heavy proteinuria, and hypertension, patients with clinically early IgAN may be expected to have a benign and nonprogressive course, and may therefore not receive the attention they need. However, even IgAN patients with a seemingly benign presentation may show a slowly progressive course, develop renal failure and eventually progress to end-stage renal disease (ESRD) after long-term follow-up. It would be important to identify these patients at an early stage to allow early treatment directed at slowing or halting progression.

We studied 177 patients with clinically early IgAN, defined by the above criteria. This study was aimed at finding useful markers that allow discrimination between patients with a progressive vs a nonprogressive course.

PATIENTS AND METHODS

Patients

In the present study, the patients were selected on the basis of findings from dipstick urinalysis at the periodical physical check-up during a period of ten years from January 1987 to May 1996. In our area, the majority of employees aged 18 to 65 years participate in periodical physical check-ups (usually twice a year). For evaluation of microscopic haematuria and/or proteinuria found by routine examination, patients are referred to the Department of Nephrology at our hospital. Next, patients are screened to rule out known causes of haematuria and/or proteinuria other than glomerular disease, such as urolithiasis and tumours as well as lesions from the lower urinary tract by performing urological investigations.
If the urinary abnormalities persist for more than three months, the patients are advised to undergo a renal biopsy. None of the patients underwent biopsies during bouts of macroscopic haematuria: at least six weeks passed between the last bout of macroscopic haematuria and the renal biopsy. For this study, the patients had to meet the following criteria: 1) the diagnosis of IgAN was established by the presence of immunohistochemical IgA deposition and electron-dense deposits predominantly in the glomerular mesangium. The amount of tissue collected for light microscopy was sufficient for diagnosis in all cases, samples with <10 glomeruli were excluded. Secondary glomerular diseases (systemic lupus erythematosus, diabetes mellitus, Schönlein-Henoch purpura, liver cirrhosis, renal allograft etc.) were excluded; 2) clinical criteria included normal renal function (defined as a glomerular filtration rate ≥90 ml/min/1.73m², estimated using the modification of diet in renal disease (MDRD) formula), proteinuria of 0.4 g/d or less, and absence of hypertension; 3) participation in healthcare tests including dipstick urine tests at least twice a year, which could help us to estimate the onset of chronic kidney disease with an error of less than six months. Controls were formed by: 1) subjects with no dipstick abnormalities (normal dipstick group) matched for age and sex; 2) subjects with dipstick abnormalities derived from the same 2023 patients and who had biopsies for the same indication as the IgAN patients, but without abnormalities in their biopsies (normal biopsy group), again matched for age and sex.

Clinical definitions

Prebiopsy duration was defined as the time from the first abnormal urinary finding to renal biopsy. The definition of haematuria was >3 red blood cells per high-power field in the urinary sediment. Proteinuria was defined as total urinary protein excretion >0.15 g/d, using 20% sulphosalicylic acid. Microalbuminuria was defined as the ratio of urinary albumin concentration to urinary creatinine with levels between 30 to 299 mg/mmol creatinine. We defined the product of urinary protein excretion (g/d) at the time of renal biopsy and prebiopsy duration (months) as UPEI. A patient was regarded as hypertensive if resting systolic blood pressure was >140 mmHg and/or diastolic blood pressure was >90 mmHg. Normal renal function was defined as a GFR ≥90 ml/ min/1.73 m², estimated using the MDRD formula.

Renal biopsy evaluation

Renal biopsy specimens were divided into three parts for light microscopy, indirect immunofluorescence, and electric microscopy, respectively. To consider the association of IgAN with thin basement membrane nephropathy, the thickness of glomerular basement membrane (GBM) was measured by the orthogonal intercept method. Glomerular lesions included mesangial proliferation, mesangial matrix widening, and glomerular sclerosis. Tubulointerstitial lesions included interstitial cell infiltration, tubular atrophy, and interstitial fibrosis. Besides, pathological evaluation also included hyaline arteriolosclerosis. All lesions were divided into normal, mild, moderate or marked (graded semiquantitatively from 0 to 3, respectively).

Follow-up assessment

During the follow-up period, the patients visited the clinic every two months. Clinical parameters taken into consideration for each patient were as follows: haematuria, proteinuria, serum creatinine level, and arterial pressure. All parameters were recorded at each clinic visit. The outcome of haematuria was divided into three categories: 1) disappearance; 2) persistent; 3) persistent with development of proteinuria. The outcome of proteinuria was divided into three groups: 1) increased, persistently more than 1 g/d; 2) remission, urinary protein excretion rate decreased to <0.15 g/d; 3) stable. Patients were classified as progressive by the development of renal insufficiency (GFR <60 ml/min/1.73 m² in the absence of therapy that reduces GFR). Patients with an urine protein >0.15 g/d and/or hypertension were treated with angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB). The indication for prednisone therapy was proteinuria >1 g/d during the follow-up period. The initial dose of oral prednisone was 40 mg/day and reduced to 20 mg/day at the end of the second month, and then slowly tapered over a two-month period. Response to prednisone treatment was defined as follows: 1) responsive: complete remission of urinary abnormalities persisting for at least two months after termination of therapy; 2) dependent: complete remission during prednisone therapy, but recurrence when the dosage was reduced under a critical level or within two months after discontinuing the treatment; and 3) resistant: no remission during ten consecutive weeks of treatment. Remission is defined as a reduction in urine protein <0.15 g/d and reduction of erythrocytes to <3 red blood cells per high-power field.

Statistical analysis

The statistical analysis was run on SPSS 10.0 software for windows. All results are expressed as mean ± SD. Student t-test or the χ² test was used in comparisons between individual groups. Logistic regression analysis was used to determine the risk factors of renal progression. Variables included were gender, age, haematuria, proteinuria at biopsy, UPEI, and pathological lesions. A p<0.05 was considered to be statistically significant.
RESULTS

Clinical and histological findings at biopsy
In the study period, 2608 patients were referred to the Department of Nephrology for evaluation of urinary abnormalities. Of these, 2602 were screened to rule out urological causes. In 280 patients the urinary abnormalities disappeared. Eventually, 2023 patients underwent a renal biopsy. Table 1 provides an overview of the renal biopsy diagnosis in relation to the urine abnormalities. Overall 177 patients with IgAN fulfilled the clinical criteria, and were classified as clinically early IgAN. Clinical characteristics of the patients and the controls are listed in Table 2. There were no statistical differences. Per definition no patients had hypertension or renal insufficiency. In the early IgAN group, 50 patients (28%) presented with pure haematuria, 28 patients (16%) with isolated proteinuria, whereas concomitant haematuria and proteinuria was the most common manifestation, in 99 patients (56%). Microalbuminuria was more common in IgAN patients. For the early IgAN group and normal biopsy group, the interval between the first detection of a urinary abnormality and the biopsy was 28 ± 14 (4 to 58) months. In the IgAN patients the thickness of GBM was 359 ± 44 nm for males and 332 ± 39 nm for females. There were no differences in GFR between patients with and without tubular atrophy, and none of the patients had hyaline arteriolosclerosis.

Postbiopsy course
The clinical course during postbiopsy follow-up is listed in Table 3. The mean follow-up duration from renal biopsy to the last outpatient check-up was 111 ± 43 (109 to 205) months. Out of 149 IgAN patients with haematuria

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**Table 1. Renal biopsy diagnosis**

<table>
<thead>
<tr>
<th></th>
<th>PH (n)</th>
<th>IP (n)</th>
<th>CHU (n)</th>
<th>Proteinuria (g/d)</th>
<th>Hypertension (n)</th>
<th>GFR (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunoglobulin A nephropathy</td>
<td>255</td>
<td>176</td>
<td>318</td>
<td>1.3 ± 0.4</td>
<td>165</td>
<td>87 ± 39</td>
</tr>
<tr>
<td>Thin basement membrane nephropathy</td>
<td>218</td>
<td>0</td>
<td>4</td>
<td>0.1 ± 0.06</td>
<td>49</td>
<td>99 ± 41</td>
</tr>
<tr>
<td>Membranous nephropathy</td>
<td>3</td>
<td>142</td>
<td>43</td>
<td>1.6 ± 0.5</td>
<td>98</td>
<td>80 ± 37</td>
</tr>
<tr>
<td>Non-IgA mesangio-proliferative glomerulonephritis</td>
<td>109</td>
<td>19</td>
<td>45</td>
<td>0.8 ± 0.4</td>
<td>36</td>
<td>95 ± 36</td>
</tr>
<tr>
<td>Focal segmental glomerular sclerosis</td>
<td>10</td>
<td>53</td>
<td>68</td>
<td>1.9 ± 0.7</td>
<td>77</td>
<td>74 ± 35</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>5</td>
<td>22</td>
<td>70</td>
<td>1.2 ± 0.4</td>
<td>18</td>
<td>86 ± 36</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td>0</td>
<td>74</td>
<td>5</td>
<td>1.7 ± 0.8</td>
<td>72</td>
<td>79 ± 37</td>
</tr>
<tr>
<td>Hypertensive nephropathy</td>
<td>1</td>
<td>51</td>
<td>3</td>
<td>0.9 ± 0.4</td>
<td>65</td>
<td>82 ± 38</td>
</tr>
<tr>
<td>Schönlein-Henoch purpura</td>
<td>13</td>
<td>9</td>
<td>33</td>
<td>1.0 ± 0.5</td>
<td>16</td>
<td>90 ± 38</td>
</tr>
<tr>
<td>Focal segmental proliferative glomerulonephritis</td>
<td>8</td>
<td>13</td>
<td>15</td>
<td>0.7 ± 0.3</td>
<td>6</td>
<td>89 ± 40</td>
</tr>
<tr>
<td>Minimal change disease</td>
<td>0</td>
<td>30</td>
<td>4</td>
<td>1.2 ± 0.6</td>
<td>1</td>
<td>91 ± 37</td>
</tr>
<tr>
<td>Sclerosing glomerulonephritis</td>
<td>0</td>
<td>12</td>
<td>8</td>
<td>2.5 ± 0.9</td>
<td>18</td>
<td>42 ± 20</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
<td>0</td>
<td>7</td>
<td>11</td>
<td>2.1 ± 0.8</td>
<td>15</td>
<td>64 ± 31</td>
</tr>
<tr>
<td>Normal biopsy</td>
<td>88</td>
<td>25</td>
<td>30</td>
<td>0.1 ± 0.05</td>
<td>2</td>
<td>98 ± 39</td>
</tr>
</tbody>
</table>

PH = pure haematuria; IP = isolated proteinuria; CHU = concomitant haematuria and proteinuria; GFR = glomerular filtration rate; ± values = ± SD.

**Table 2. Clinical data at the time of renal biopsy**

<table>
<thead>
<tr>
<th></th>
<th>Early IgAN</th>
<th>Normal biopsy</th>
<th>Normal dipstick</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>177</td>
<td>135</td>
<td>120</td>
</tr>
<tr>
<td>Female /male (n)</td>
<td>69/108</td>
<td>40/95</td>
<td>37/83</td>
</tr>
<tr>
<td>Age (years)</td>
<td>38 ± 16</td>
<td>38 ± 15</td>
<td>37 ± 16</td>
</tr>
<tr>
<td>Prebiopsy duration (months)</td>
<td>27 ± 15</td>
<td>28 ± 14</td>
<td></td>
</tr>
<tr>
<td>Presentation:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>· Pure haematuria</td>
<td>50</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>· Isolated proteinuria</td>
<td>28</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>· Combined haematuria and proteinuria</td>
<td>99</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>124 ± 11</td>
<td>123 ± 10</td>
<td>127 ± 12</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>73 ± 10</td>
<td>74 ± 11</td>
<td>72 ± 10</td>
</tr>
<tr>
<td>Urinary protein excretion (g/d)</td>
<td>0.24 ± 0.11</td>
<td>0.23 ± 0.09</td>
<td>0.05 ± 0.05</td>
</tr>
<tr>
<td>Microalbuminuria (n)</td>
<td>133</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Normoalbuminuria (n)</td>
<td>44</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min/1.73 m²)</td>
<td>100 ± 23</td>
<td>102 ± 22</td>
<td>102 ± 21</td>
</tr>
</tbody>
</table>

± Values = ± SD.
at presentation, the haematuria disappeared in 18 and persisted in 131 patients. In addition, four patients with isolated proteinuria developed haematuria. Twelve patients with IgAN and isolated haematuria developed proteinuria, and proteinuria increased to values >1 g/d in 14 out of 28 patients with isolated proteinuria and in 53 of 99 patients with combined haematuria and proteinuria. Proteinuria disappeared in only two out of 28 and eight out of 99 patients respectively. From Table 3 it is evident that urine abnormalities disappeared in more than half of the patients with a normal biopsy.

Patients with IgAN developed hypertension more frequently. Renal insufficiency was only observed in patients with IgAN and developed in 43 (24%) of the patients. No patient thus far has reached ESRD. The initial presentation of patients with renal insufficiency was pure haematuria in eight, concomitant haematuria and proteinuria in 27, and isolated proteinuria in eight patients. All patients with renal insufficiency had proteinuria; in 39 the urine protein was >1 g/d.

During the follow-up period, 138 patients with urine protein >0.15 g/d and/or hypertension were treated with ACEI and/or ARB. Of the 138 patients, 130 patients were in the early IgAN group, five patients were in the normal biopsy group, and three patients were in the normal dipstick group.

During the course of the follow-up, 79 early IgAN patients with increasing proteinuria (proteinuria increased to more than 1 g/d) were advised to start treatment with prednisone, and 52 of the 79 patients agreed to receive immunosuppressive therapy. Of the 52 patients, four complained of some unbearable side effects of the medication such as gastric discomfort, two patients had severe complications such as serious infections. Finally, seven patients were forced to abandon immunosuppressive therapy, and the 45 patients left were completely followed up. Regarding the response to prednisone therapy, 30 patients responded, nine patients were prednisone-dependent, and six patients were resistant.

### Table 3. Clinical data at the end of follow-up

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>Early IgAN</th>
<th>Normal biopsy</th>
<th>Normal dipstick</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematuria:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disappearance</td>
<td>18 (10%)</td>
<td>67 (50%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Persistent</td>
<td>135 (76%)</td>
<td>41 (38%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Proteinuria:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>10 (6%)</td>
<td>90 (67%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Stable</td>
<td>50 (28%)</td>
<td>14 (10%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Increased</td>
<td>79 (46%)</td>
<td>3 (3%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>68 (38%)</td>
<td>11 (8%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>43 (24%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

### Table 4. Risk factors for renal progression

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>P value</th>
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<tbody>
<tr>
<td>Gender</td>
<td>0.616</td>
<td>0.897</td>
</tr>
<tr>
<td>Age</td>
<td>1.387</td>
<td>0.742</td>
</tr>
<tr>
<td>Haematuria</td>
<td>2.734</td>
<td>0.041</td>
</tr>
<tr>
<td>Proteinuria at biopsy</td>
<td>2.035</td>
<td>0.356</td>
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<tr>
<td>Urinary protein excretion index</td>
<td>3.127</td>
<td>0.038</td>
</tr>
<tr>
<td>Mesangial proliferation</td>
<td>1.495</td>
<td>0.636</td>
</tr>
<tr>
<td>Mesangial matrix widening</td>
<td>0.839</td>
<td>0.762</td>
</tr>
<tr>
<td>Glomerular sclerosis</td>
<td>1.996</td>
<td>0.352</td>
</tr>
<tr>
<td>Interstitial cell infiltration</td>
<td>5.317</td>
<td>0.014</td>
</tr>
<tr>
<td>Tubular atrophy</td>
<td>4.235</td>
<td>0.028</td>
</tr>
<tr>
<td>Interstitial fibrosis</td>
<td>2.096</td>
<td>0.091</td>
</tr>
</tbody>
</table>

**DISCUSSION**

In mass screening of healthy adults, the positive rate of urinary abnormalities is extremely high. For haematuria, 1.2 to 21.1% of the subjects were positive, and 0.4 to 4.9% of the subjects were positive for proteinuria using dipstick analysis of urine. In our area, 8.5% of the subjects were positive for haematuria and 3.1% were positive for proteinuria. Our policy has been to perform a renal biopsy in a patient with persistent urinary abnormalities for more than three months after exclusion of nonglomerular diseases. Most of these patients in our cohort would not have undergone renal biopsy in many parts of the world. However, our patients fulfill the definition of chronic kidney disease (CKD) stage I, since the duration of urinary abnormalities was more than three months. Primary chronic glomerulonephritis is the most common cause of primary renal disease worldwide. Ultimately up to 40% of patients may progress to chronic renal failure, and spontaneous remission is distinctly uncommon. The clinical onset of primary chronic glomerulonephritis can be silent, and is often manifested by asymptomatic urinary abnormalities. However, even patients with...
With respect to the association between the number of clinically early IgAN and renal function is recommended for the patients with regular monitoring of blood pressure, proteinuria and 38% of the patients, and 24% of the patients suffered however, during the follow-up period, we did find that at presentation due to the inclusion criteria of this study. None of our patients had poor prognostic factors such as isolated proteinuria developed haematuria, and finally of glomerular inflammation in the early course of renal disease. Association of haematuria with renal function progression was only observed in patients with initially normal renal function. It seems that the prognostic value of haematuria is greater in the early stage of IgAN. Of note, we observed that four patients with initially an value of haematuria is greater in the early stage of IgAN. The rising level of urinary erythrocytes and renal outcome, there is no firm conclusion. Our results suggested that haematuria played an unfavourable role in the course of IgAN. The rising level of urinary erythrocytes might indicate a high degree of glomerular inflammation in the early course of renal disease. Association of haematuria with renal function progression was only observed in patients with initially normal renal function. It seems that the prognostic value of haematuria is greater in the early stage of IgAN. Of note, we observed that four patients with initially an isolated proteinuria developed haematuria, and finally three of them were classified into the progressive group. It has been well documented that high-grade proteinuria is a risk factor for poor outcomes. However, in the present study, the level of proteinuria at the time of renal biopsy was no more than 0.4 g/d, so it had limited value in predicting probability of developing renal progression. On the other hand, we found that UPEI (defined as the product of urinary protein excretion at the time of renal biopsy and prebiopsy duration) may be a valuable marker for predicting renal progression. Considering that proteinuria contributes to renal damage, we speculated that this result might depend on the amount of proteinuria from the onset of the disease to the time of renal biopsy. Moreover, it has been reported that patients with progressive proteinuria during the course were more liable to have renal function deterioration than those with proteinuria at the beginning. As mentioned above, in our research, we could identify the time of onset of IgAN with an error of less than six months. Hence, the accumulation of proteinuria could be an important prognostic factor for renal progression in IgAN, and we are able to approximately estimate it by UPEI.

In the present study, the interstitial lesions, mainly interstitial cell infiltration and tubular atrophy, were better prognostic indicators for renal outcome as compared with the glomerular lesions. Our data are in agreement with those of other authors. They advocate tubulointerstitial changes as the most reliable predictor of chronic and irreversible renal damage in chronic glomerular diseases, as were some other parameters such as proteinuria. In this regard, it has been well documented that tubular lesions reflect the ability of interstitial processes to damage normal glomeruli and to contribute to a greater nephron loss.

The prevalence of IgAN differs greatly between geographic locations, being 29.2% of the biopsied population in Asia, 12% in Australia, 10.7% in Europe and 5% in North America, so IgAN is more prevalent in Asian countries including China. Moreover, unlike in developed countries, primary chronic glomerulonephritis other than hypertensive nephropathy and diabetic nephropathy is the leading cause of ESRD in developing countries. Therefore, it is uncertain how applicable the results in Chinese subjects are for people from other regions in the world.

**Conclusion**

Our observations suggest that renal progression may occur in a considerable number of patients with clinically early IgAN. We further highlight that haematuria. UPEI or tubulointerstitial lesions might be useful markers to identify high-risk patients with renal progression. It may add extra information to identify people at a high risk for developing renal insufficiency, who may benefit from preventive strategies, early therapy and closer follow-up.
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Papillary carcinoma in struma ovarii: an unusual presentation

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ABSTRACT

Struma ovarii is the presence of thyroid tissue as the major cellular component in an ovarian tumour. Papillary carcinoma in struma ovarii is exceptionally rare. We report a case of papillary carcinoma in struma ovarii in a postmenopausal 51-year-old female who initially presented clinically with hyperthyroidism. Serology, however, did not confirm hyperthyroidism. During a re-admission to our hospital later that year she appeared to have had periods of postmenopausal vaginal haemorrhage. An abdominal mass was located by radiography and pathological investigation revealed a papillary carcinoma in struma ovarii. Some striking features of this unusual presentation of importance to the internal medicine physician are discussed.

KEYWORDS

Papillary carcinoma, review, struma ovarii

INTRODUCTION

Struma ovarii is defined as a teratoma of the ovary, totally or predominantly composed of thyroid tissue.1 Approximately 2.5% of cystic teratomas are struma ovarii.1 Teratomas, by definition, may contain endodermal and mesodermal tissue, which can also involve endocrine tissue. Generally this endocrine tissue does not secrete significant amounts of thyroxine. However, in 5 to 10% of cases patients may present with manifest hyperthyroidism due to a thyroid adenoma in the struma.4 Functional struma ovarii should be considered as a possible cause of thyrotoxicosis in a woman with hyperthyroidism who has no goitre.3 As with cervical thyroid tissue, ectopic thyroid tissue can undergo carcinomatous changes. Thyroid carcinoma in struma ovarii is extremely rare.4 The patient we report here presents with rare complications of struma ovarii. In addition, the atypical presentation misled us when making our diagnosis.

CASE REPORT

A 51-year-old female first came to our attention with the clinical suspicion of hyperthyroidism, diabetes mellitus type 2 de novo and postmenopausal vaginal haemorrhage. At that time she was admitted to our hospital because of respiratory failure following pneumococcal pneumonia. Her medical history revealed chronic obstructive pulmonary disease (COPD) and premature menopause at 38 years of age. Four years later she had undergone curettage because of postmenopausal vaginal haemorrhage.

There was suspicion of hyperthyroidism since she had unwillingly lost over 10 kg in a three-month period, suffering from fatigue, generalised anxiety and depression. Clinical examination of the thyroid showed no abnormalities. Laboratory findings showed normal haematology, liver and kidney function testing. Biochemically there was no evidence of hyperthyroidism with free thyroxine (fT4) 11 pmol/l (normal 10 to 25 pmol/l); triiodothyronine (T3) 1.3 nmol/l (normal 1.3 to 3.0 nmol/l) and antithyroid peroxidase antibody (anti-TPO) <10 U/ml (normal 0 to 35 U/ml). The thyroid-stimulating hormone (TSH), however, was surprisingly low at 0.01 mU/l (normal 0.2 to 4.2 mU/ml). The hyperglycaemia proved to be steroid related and was treated with glimepiride 2 mg once daily. The postmenopausal vaginal haemorrhage was regarded secondary to discontinuing tibolone, which she had been using for several years since the menopause. Digital pelvic
examination, speculum examination and transvaginal ultrasound were unremarkable. CA-125 was 15.7 kU/l (normal <20 kU/l) and the carcinoembryonic antigen was 3.3 µg/l (normal <5 µg/l). Tibolone was restarted.

One year later she was readmitted to our hospital suffering from an exacerbation of chronic obstructive pulmonary disease. A short episode of postmenopausal vaginal haemorrhage reoccurred during her admission. Transvaginal ultrasound revealed a large mass in the left lower posterior abdomen originating from the left adnexum. Some ascites was detected. A computed tomography (CT) scan of the abdomen showed a large, lobed, multicystic, nodular pelvic mass with contrast enhancement in the small pelvis, associated with either the left or the right adnexum, or both. The tumour may have been connected to the sigmoid colon. Locally as well as para-aortally small non-pathological lymph nodes were seen (Figure 1). No other abnormalities were found. Ultrasound of the thyroid showed normal thyroid dimensions and an irregular aspect of the left thyroid lobe. Scintigraphy revealed some ‘cold’ areas in the right and left lobe.

During laparotomy exploration of the uterus and left adnexum showed no abnormalities. The right adnexum was enlarged at 10 x 8 x 6 cm and right adnexal torsion was found. Curettage of the uterus showed no abnormalities but the vagina canal was atrophic and bleed easily. Frozen section analysis of the right adnexum was performed. On pathological macroscopic examination the right ovary appeared to be enlarged (diameter 10 cm) with a nodular surface. On the cut surface it had a brown-red spongy, partly cystic appearance. Frozen section analysis showed struma ovarii. There was no indication of malignancy at that time. Further analysis (postoperatively), however, showed struma ovarii with a focus of papillary carcinoma (Figure 2). Furthermore, a benign Brenner tumour was found in both adnexa. The partially resected omentum showed no evidence for malignancy.

When the final diagnosis was reached the patient was informed about the diagnosis of malignant struma ovarii, the necessary re-staging procedure, and the prognosis of her disease. Taking her clinical condition with low pulmonary reserve into account and in accordance with the patient’s wishes no further surgical intervention or chemotherapy was performed.

In the follow-up period she did not have any vaginal haemorrhage or signs of hyperthyroidism. Levels of TSH, T3 and T4 normalised swiftly (Table 1). Four years later she died of respiratory failure due to severe chronic obstructive pulmonary disease and persistent smoking. High-resolution CT scanning of the lungs and repeated X-rays of the thorax in the past four years had still not shown evidence of malignancy.

**DISCUSSION**

This case showed an unusual presentation of malignant struma ovarii with postmenopausal haemorrhage. To our knowledge this has only been described once before. Although there was some suspicion clinically for hyperthyroidism at an earlier stage this could not be confirmed by biochemical testing. At first presentation subnormal plasma TSH levels were repetitively measured.
A thyroid-releasing hormone (TRH) test appeared to be normal. This may have indicated ectopic thyroglobulin production which could not be detected in our immunoassay. Therefore T₃ and fT₄ might have appeared to be in the normal range. Discordant findings of serum thyroglobulin in patients with papillary thyroid carcinoma have been described before. After bilateral ovariectomy the TSH, T₃ and fT₄ levels completely normalised (table 1).

Retrospectively, our patient had had a previous episode of vaginal haemorrhage five months before. Physical examination as well as transvaginal ultrasound at that time had shown no abnormalities. This suggests that the tumour, which was large at the time of surgery, had progressed rapidly.

Malignant struma ovarii is exceptionally rare. It generally occurs in the fifth decade of life and preferentially affects the left rather than the right ovary for unknown reasons. Recently all reported cases, a total of 39 cases up till 2004, were reviewed. The average age at presentation was 44. Patients predominately presented with a pelvic mass (45%), abdominal pain (40%), menstrual irregularities (9%) and hyperthyroidism (5%). Papillary carcinoma was the most common (44%) histopathological finding followed by follicular carcinoma (30%) and the follicular variant of papillary carcinoma (26%). Metastasis was seen in nine cases (23%), recurrence occurred in six cases (15%). The average time to detection of recurrence was four years. Owing to its rarity, there has been some controversy about the diagnosis and treatment of patients with malignant struma ovarii. The preoperative diagnosis of struma ovarii may be possible through thyroglobulin measurement or scanning in patients affected by hyperthyroidism, but the majority of patients are diagnosed postoperatively as was the case in our patient. The histological criteria for malignancy include increased cellularity and cellular atypia. Thyroid carcinoma metastasised to the ovary can be confused with true struma ovarii. Struma ovarii may cause elevated CA-125 and ascites, as was the case in our patient, which is usually nonmalignant.

Because of the rarity of such cases and the difficulties related to preoperative diagnosis, the management of malignant struma ovarii has not been clearly defined.

Some authors have suggested a management as used for other germ cell tumours. Others have proposed that malignant struma ovarii should be treated like its thyroid counterpart. For women of childbearing age, conservative management could be warranted, although there are not enough data available.

After completion of childbearing, treatment should consist of total abdominal hysterectomy, bilateral salpingo-oophorectomy and staging in the usual fashion. Our patient, however, suffered from severe COPD and was a persistent smoker. In 1999 she was admitted to the intensive care unit and needed mechanical ventilation due to respiratory insufficiency following pneumococcal pneumonia and sepsis. In the following four months she was readmitted to our hospital four times with an exacerbation of COPD and had developed steroid-induced diabetes. When the final diagnosis was reached the patient was informed about the diagnosis of malignant struma ovarii, the necessary re-staging procedure, and the prognosis of her disease. Taking her clinical condition with low pulmonary reserve into account and in accordance with the patient’s wishes no further surgical intervention or chemotherapy was performed.

A variety of postoperative treatments can be considered; however, most patients do not undergo adjuvant therapy following initial surgery. Thyroidectomy and ablation with radioiodine (¹³¹I) are necessary for treating advanced disease. Malignant struma ovarii appears to have a good prognosis. The metastatic potential is low.

**Conclusions**

Malignant struma ovarii is a medical rarity. This is the second report of a presentation with postmenopausal vaginal haemorrhage. Although no biochemical evidence was found there was clinical suspicion for hyperthyroidism, due to ectopic thyroglobulin production by the struma ovarii. Radiographic follow-up suggests that the tumour had progressed very rapidly, which has not been described before. The postmenopausal vaginal haemorrhage may have been partially due to vaginal atrophy as was observed.
during surgical exploration. More likely this presentation is
caued by tumour progression in the small pelvis without
over uterus pathology.

ACKNOWLEDGEMENT

We thank Dr A.H.L. Mulder, clinical chemist, Twenteborg
Hospital Almelo for her contributions.

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We describe a case of hypokalaemic hypertension due to hyperaldosteronism caused by a unilateral adrenocortical tumour with unfavourable histopathology suggestive of malignancy. After removal, the aldosterone excess disappeared. The patient’s clinical course was uneventful, until she presented with extensive metastases of adrenal carcinoma four years later. Biochemical abnormalities were now consistent with glucocorticoid excess without hyperaldosteronism. She died four months later. Although malignant aldosterone-producing adrenal tumours are very rare, the present case underscores that primary hyperaldosteronism can occur in the context of adrenocortical carcinoma.

ABSTRACT

We describe a case of hypokalaemic hypertension due to hyperaldosteronism caused by a unilateral adrenocortical tumour with unfavourable histopathology suggestive of malignancy. After removal, the aldosterone excess disappeared. The patient’s clinical course was uneventful, until she presented with extensive metastases of adrenal carcinoma four years later. Biochemical abnormalities were now consistent with glucocorticoid excess without hyperaldosteronism. She died four months later. Although malignant aldosterone-producing adrenal tumours are very rare, the present case underscores that clinicians should be aware that primary hyperaldosteronism can occur in the context of adrenocortical carcinoma.

KEYWORDS

Adrenal carcinoma, aldosterone, hypertension, hypokalaemia

INTRODUCTION

As the criteria for evaluation of hyperaldosteronism are being broadened, aldosterone excess is increasingly diagnosed as the cause of hypertension. Hyperaldosteronism is generally due to an aldosterone-producing adenoma of the adrenal gland (APA) or to bilateral adrenal hyperplasia. Adrenocortical carcinomas are rare with an estimated incidence of only 0.5 to 2 per one million people per year, and the occurrence of hyperaldosteronism due to a malignant adrenal tumour is even less frequent. In a large series of adrenocortical carcinomas, only 2.5% had developed hyperaldosteronism. Conversely, it has been estimated that hyperaldosteronism is due to adrenocortical carcinoma in only 1% of patients. When a malignant adrenocortical carcinoma is suspected, surgical removal should be performed as early as possible, and postoperative adjuvant medical therapy may be warranted in case of malignancy.

We describe a case of hyperaldosteronism due to a unilateral adrenocortical tumour with unfavourable histopathology. The aldosterone excess disappeared postoperatively, but the patient subsequently presented with metastatic adrenocortical carcinoma and biochemical signs of glucocorticoid excess without reoccurrence of hyperaldosteronism. The case presented here underscores that clinicians should be aware that aldosterone-producing adrenal tumours can bear malignant potential.

CASE REPORT

A 52-year-old woman without clinical signs suggestive of Cushing’s syndrome was referred for evaluation of hypokalaemic hypertension. Her blood pressure was 190 mmHg systolic and 100 mmHg diastolic. Laboratory investigation showed hypokalaemia (3.0 mmol/l), increased urinary potassium and elevated serum aldosterone (0.80 nmol/l; normal: <0.60 nmol/l) with suppressed plasma renin activity (0.14 nmol/l/h). Urinary aldosterone-glucuronide excretion after salt loading was increased (51 nmol/24 h; normal <34 nmol/24 h). Morning serum cortisol as well as urinary excretion of cortisol metabolites and metanephrines were not elevated. Magnetic resonance imaging showed a 4 cm inhomogeneous mass of the right adrenal (figure 1). APA was suspected.
At surgery, an adrenal mass (51 grams) was removed, which was encapsulated and lobulated, with a small margin of normal adrenal tissue. Histopathological examination showed fields of tumour cells, separated by strands of fibrovascular stroma with focal necrosis and calcification. Completely diffuse (40%) areas were present. The tumour infiltrated its capsule and sinusoidal invasion was present. Generally, 13 to 16 mitotic cells/50 high power fields were seen (figure 2). The hypokalaemia resolved postoperatively and her blood pressure decreased. The serum aldosterone normalised. One year later, an abdominal ultrasound did not reveal any abnormalities. After two years, the patient appeared healthy and was then referred to her primary physician. Four years postoperatively, she developed hepatomegaly and her blood pressure had increased. There were no signs of virilisation. Serum potassium, aldosterone (0.2 nmol/l) and plasma renin activity (1.4 nmol/l/h) were normal. Serum cortisol at 8 a.m. was rather high (740 nmol/l), as were serum levels of the cortisol precursor 11-deoxycortisol and testosterone. Plasma ACTH was low. Urinary free cortisol (864 (normal <270) nmol/24 h) and androgen metabolite excretion were increased, and abnormal steroid metabolites were present. These findings were consistent with glucocorticoid and androgen excess without hyperaldosteronism. Computer tomography demonstrated a large right-sided adrenal tumour growing into the liver and possibly the right kidney, multiple metastases in the liver and lungs and mediastinal lymphadenopathy. Histopathological investigation showed hepatic metastasis of adrenal carcinoma. Palliative therapy with mitotane was initiated, which was poorly tolerated and not effective. Ascites developed which had to be removed. There were no malignant cells on cytological investigation. The patient died four months later.

**DISCUSSION**

Consequent to more frequent use of abdominal imaging techniques, adrenocortical tumours, including those bearing malignant potential, are increasingly recognised. Nonetheless, adrenocortical carcinomas are not yet being diagnosed earlier, nor has their survival improved. Adrenal carcinomas producing excess aldosterone are very rare, with only 58 patients being reported. Adrenocortical carcinomas have a bi-modal age distribution, and occur more frequently in women. In a review comprising 602 cases of adrenocortical carcinomas, Ng stated that 62% of these tumours are functional. Glucocorticoid excess was found most frequently. In 114 sporadic adrenal tumours,
mineralocorticoid excess as the only sign of hormonal overproduction was observed in none of 18 malignant tumours. In the patient presented here hyperaldosteronism was demonstrated at presentation. There were no clinical signs of Cushing’s syndrome initially, and limited laboratory studies did not show glucocorticoid excess. Upon recurrence of the tumour, serum aldosterone was not elevated and plasma renin activity was not suppressed. Urinary excretion of free cortisol and glucocorticoid metabolites were now increased, whereas plasma ACTH was low. Furthermore, high plasma and urinary levels of abnormal glucocorticoid metabolites were demonstrated, as were increased concentrations of androgens and urinary androgen metabolites. These findings are consistent with the possibility that the type of adrenal hormonal overproduction can change during the course of the disease. This phenomenon has only been described a few times before, and could be due to modifications in the expression of specific steroidogenic enzymes during tumour dedifferentiation, together with (relative) blocks of enzymes involved in adrenal hormonogenesis. Whether an adrenal cortical tumour is malignant can only be ascertained unequivocally in case of metastases. Of the histological classification systems, the (modified) Weiss criteria have been used most widely. Using this classification, three findings were only found in malignant tumours: venous invasion, mitotic rate >5 per 50 HPFs and atypical mitotic figures, two of three criteria being present in the current tumour. The Weiss score was found to be a prognostic factor for disease-free survival, independently of tumour size and functional status. This system has been modified, resulting in a sensitivity of 96% for malignancy. According to these criteria, the present tumour had a very high score (table 1). Tumour size is also helpful to predict malignancy. Adrenal carcinomas are larger, and a cut-off size of 4 to 6 cm has been proposed as criterion for removal in incidentally discovered tumours. At presentation, mean size of adrenocortical carcinoma has been reported to be 11.8 to 14 cm, and 84% of these tumours weigh >100 g. In comparison, mean maximal tumour diameter is 7.0 cm in aldosterone-producing adrenocortical carcinomas, whereas in APA mean tumour size is 2.2 cm. Thus, in general malignant aldosterone-producing tumours appear to be larger than APAs and smaller than adrenal cortical carcinomas. Finally, an algorithm has been proposed using tumour density to ascertain the likelihood of malignancy. An irregular shaped tumour >4 cm, with intermediate to high-signal intensity on T2-weighted MRI or high unenhanced CT attenuation values is most likely malignant. Benign tumours are usually <4 cm in diameter, have a smooth, round appearance, are homogeneous and have a low density value. The patient reported here corroborates that clinicians should be aware that primary hyperaldosteronism can occur in the context of adrenocortical carcinoma.

Table 1. Modified Weiss classification system with scoring for the tumour of the present patient

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<tr>
<th>Weight of criteria</th>
<th>Present case</th>
<th>Present case score</th>
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<tr>
<td>Mitotic rate &gt;5/50 HPF</td>
<td>2</td>
<td>13 mitotic cells per 50 high power fields</td>
</tr>
<tr>
<td>≤25% clear cells</td>
<td>2</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Abnormal mitoses</td>
<td>1</td>
<td>Absent</td>
</tr>
<tr>
<td>Capsular invasion (tumour capsule)</td>
<td>1</td>
<td>Present</td>
</tr>
<tr>
<td>Necrosis</td>
<td>1</td>
<td>Present</td>
</tr>
<tr>
<td>Nuclear grade</td>
<td>-</td>
<td>Grade IV</td>
</tr>
<tr>
<td>Fürhmann III/IV</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>&gt;1/3 diffuse architecture</td>
<td>-</td>
<td>Present</td>
</tr>
<tr>
<td>Venous invasion</td>
<td>-</td>
<td>Absent</td>
</tr>
<tr>
<td>Sinusoidal invasion</td>
<td>-</td>
<td>Present</td>
</tr>
<tr>
<td>Total score</td>
<td>0-7</td>
<td>6</td>
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*Malignancy threshold: value ≥3 points.

Remarkably, metastases may develop without re-occurrence of hyperaldosteronism. Whether postoperative adjuvant medical treatment and close long-term follow-up beneficially affect prognosis is still uncertain.

REFERENCES


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MONTHLY NJM ONLINE HITLIST

The table lists online hits for all articles published in the March issue of the Netherlands Journal of Medicine (available online on Pubmed since 18 March 2008).

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Alma, et al. Malignant aldosterone-producing adrenal tumour.

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Goserelin-induced transient thyrotoxicosis in a hypothyroid woman on L-thyroxine replacement

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ABSTRACT

An increase in free thyroxine (fT4) and a decrease in thyroid-stimulating hormone (TSH) was observed in a hypothyroid woman on levothyroxine treatment after implantation of goserelin, a gonadotropin-releasing hormone (GnRH) analogue. In the literature no data are available that describe a drug interaction between GnRH analogues and thyroid hormone replacement. Our hypothesis to explain this observation is that goserelin decreased serum thyroxine-binding-globulin (TbG), resulting in an increase in fT4 and thereby a decrease in serum TSH.

KEYWORDS

GnRH analogue, hypothyroidism, sex hormones, thyroid function

INTRODUCTION

Sometimes patients ask their doctors questions about drug interactions, which are hard to answer because the literature contains insufficient data on the particular topic. In our case, the question was if there was a known drug interaction between thyroxine and goserelin, a gonadotropin-releasing hormone (GnRH) analogue. Nothing could be found in the literature on such an interaction. Subcutaneous implantation of goserelin will suppress luteinising hormone (LH) and follicle-stimulating hormone (FSH) via sustained delivery of GnRH, resulting in a decrease in oestrogens and chemical castration. The question from our patient, who was on levothyroxine replacement because of primary hypothyroidism, led us to hypothesise that in her case goserelin administration could indeed have an adverse interaction with thyroxine treatment. For, the fall in serum oestrogens will decrease the serum concentration of thyroxine-binding globulin (TBG), the major transport protein for thyroid hormones in serum. Consequently less thyroid hormone is needed for TBG binding. If the thyroid gland is unable to decrease its thyroxine secretion (as in our patient), continuation of the exogenous dose of thyroxine might result in an increase of serum free thyroxine (fT4). This case report tests our hypothesis that this indeed might happen.

CASE REPORT

A 41-year-old woman with Hashimoto’s hypothyroidism, euthyroid on 100 mg thyroxine for several years, was seen at our outpatient clinic. She suffered from metrorrhagia and had tried several hormonal treatment modalities without success. The next step would be subcutaneous implantation of goserelin to induce chemical castration. She was concerned about a possible interaction between thyroxine and goserelin (Zoladex), a GnRH analogue. In view of our hypothesis that the thyroxine replacement dose might become too high we decided to control her thyroid function two weeks after implantation and planned a visit one week thereafter. The thyroxine replacement dose was not changed. One week after administration of goserelin, she complained of tingling in arms and neck, flushes and hyperhydrosis. The general practitioner administered nitroglycerine, the tingling in the arms wore off and she was admitted to a cardiac care unit elsewhere. Ischaemic cardiac disease was not diagnosed; thyroid function was not measured.
We hypothesised that an elevated fT4 might occur after total T4 decreased significantly in both groups within four weeks after implantation of goserelin. Two weeks after implantation the fT4 had increased to 27.4 pmol/l with a fall of thyroid-stimulating hormone (TSH) to 0.31 mU/l. The TBG was reduced from 330 nmol/l to 290 nmol/l and serum oestradiol was suppressed below 0.04 nmol/l. Three weeks after implantation of goserelin, the fT4 was normal (20 pmol/l); TSH was still decreased and normalised later. TBG and oestradiol were not measured at that time. After seven weeks of implantation, the TBG concentration was 300 nmol/l and the oestradiol normalised to 0.16 nmol/l. Triiodothyronine (T3) did not change during the observation period. The goserelin implantation was not repeated because of her symptoms.

Figure 1 shows the results of her thyroid function during a follow-up of 12 weeks after implantation of goserelin. Two weeks after implantation the fT4 had increased to 27.4 pmol/l with a fall of thyroid-stimulating hormone (TSH) to 0.31 mU/l. The TBG was reduced from 330 nmol/l to 290 nmol/l and serum oestradiol was suppressed below 0.04 nmol/l. Three weeks after implantation of goserelin, the fT4 was normal (20 pmol/l); TSH was still decreased and normalised later. TBG and oestradiol were not measured at that time. After seven weeks of implantation, the TBG concentration was 300 nmol/l and the oestradiol normalised to 0.16 nmol/l. Triiodothyronine (T3) did not change during the observation period. The goserelin implantation was not repeated because of her symptoms.

The opposite study was done several years later. Thirty-six postmenopausal women were given oral oestrogens. In both groups TBG and total T4 became significantly elevated after 12 weeks but in the healthy group TSH and fT4 did not change. In the hypothyroid women on thyroxine replacement fT4 and TSH were significantly decreased and elevated, respectively, at 12 weeks; one woman had symptoms of hypothyroidism and needed an increase in levothyroxine replacement dose. This effect persisted during the whole study period. No data were shown after discontinuation of oestrogens.

The difference in fT4 and TSH between the control groups and the women on thyroxine is explained by the notion that subjects on levothyroxine replacement are not able to adjust their serum fT4 concentration via changes in the TSH secretion. For example, administration of androgens will decrease TBG, in all likelihood due to a decrease of glycosylation of TBG and thereby an increase in the clearance of TBG. According to the law of mass action, the reduction in TBG will increase the free fraction of circulating thyroxine (fT4), followed by a decrease in TSH secretion. Under physiological conditions the lower TSH secretion will reduce thyroxine secretion by the thyroid gland, and the equilibrium between bound and fT4 in the circulation is restored under normalisation of serum fT4.

In hypothyroid patients on a fixed dose of exogenous thyroxine the adaptation to changes in serum TBG via the negative feedback of thyroid hormones on the pituitary is failing. Upon administration of androgens to women the decrease in TBG concentration as reported by Arafah is between 9 to 13 mg/l (167 to 241 nmol/l). The TBG level in our patient decreased by only 40 nmol/l upon suppression of endogenous oestrogens. Thus the decrease in our patient was modest and may explain the limited increase in fT4 and minimal decrease in TSH. The effect of sex hormone therapy on thyroid function depends on the route of administration. Transdermal oestrogens or testosterone therapy do not raise serum TBG and therefore do not alter the fT4 level, because transdermal sex hormones do not have a hepatic first-pass effect in contrast to oral sex hormones. Thus the transdermal route is preferable in women receiving thyroid-hormone replacement. TBG and T4 are also influenced by tamoxifen, droloxifene and by intramuscular testosterone (table 1). No data of alterations in fT4 due to tamoxifen or intramuscular

**DISCUSSION**

We hypothesised that an elevated fT4 might occur after implantation of goserelin which might necessitate a lowering of the thyroxine replacement dose. Our observation in the patient supported the hypothesis: fT4 levels increased and TSH became suppressed. The causal role of the decrease in serum TBG is supported by data from the literature. Baha and Arafah studied two groups of women with breast cancer: women with normal thyroid function and hypothyroid who were adequately substituted with levothyroxine replacement. Both groups were treated with the oral androgen, fluoxymesterone. Serum TBG and total T4 decreased significantly in both groups within four and two weeks, respectively. In the control group fT4 levels remained unchanged and TSH decreased slightly. In the hypothyroid group on levothyroxine replacement fT4 levels increased and TSH decreased within two weeks. These biochemical changes were associated with complaints of tachycardia, hyperhydrosis and insomnia. Thyroid hormone doses had to be reduced by between 25 and 50% to maintain euthyroidism. After discontinuation of the androgens, the TSH levels increased and fT4 levels decreased when patients continued on the same thyroxine dose. TBG levels returned to normal after eight to ten weeks after therapy was discontinued.

Upon administration of androgens to women the decrease in TBG concentration as reported by Arafah is between 9 to 13 mg/l (167 to 241 nmol/l). The TBG level in our patient decreased by only 40 nmol/l upon suppression of endogenous oestrogens. Thus the decrease in our patient was modest and may explain the limited increase in fT4 and minimal decrease in TSH. The effect of sex hormone therapy on thyroid function depends on the route of administration. Transdermal oestrogens or testosterone therapy do not raise serum TBG and therefore do not alter the fT4 level, because transdermal sex hormones do not have a hepatic first-pass effect in contrast to oral sex hormones. Thus the transdermal route is preferable in women receiving thyroid-hormone replacement. TBG and T4 are also influenced by tamoxifen, droloxifene and by intramuscular testosterone (table 1). No data of alterations in fT4 due to tamoxifen or intramuscular
testosterone are known in patients with hypothyroidism. But it can be assumed that fT4 levels would change in substituted hypothyroidism. The clinical relevance of these changes is minor in many but not all patients as shown by Arafah.1,2 The symptoms in our patient after goserelin implantation are, in our opinion, non-thyroid-related side effects. First TSH was not completely suppressed and second, T3 remained unchanged.

### Table 1. The effect of exogenous oestrogens and androgens on thyroid function tests

<table>
<thead>
<tr>
<th></th>
<th>TBG</th>
<th>T4</th>
<th>Free T4</th>
<th>TSH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral oestrogens</td>
<td>↑</td>
<td>↑</td>
<td>=</td>
<td>↓ (Hypo on T4) ↑ (Hypo on T4)</td>
</tr>
<tr>
<td>Transdermal oestrogens</td>
<td>=</td>
<td>=</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Tamoxifen, droloxifene</td>
<td>↑</td>
<td>↑</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Oral androgens</td>
<td>↓</td>
<td>↓</td>
<td>=</td>
<td>↑ (Hypo on T4) ↓ (Hypo on T4)</td>
</tr>
<tr>
<td>Intramuscular testosterone</td>
<td>↓</td>
<td>↓</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Transdermal testosterone</td>
<td>=</td>
<td>=</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Goserelin</td>
<td>↓</td>
<td>↓</td>
<td>↑ (Hypo on T4)</td>
<td>↓ (Hypo on T4)</td>
</tr>
</tbody>
</table>

TBG = thyroxine-binding globulin; T4 = thyroxine; TSH = thyroid-stimulating hormone.

### CONCLUSION

Our advice is to check thyroid function regularly in patients on thyroid hormone substitution therapy who are being treated with sex hormones.

### REFERENCES

3. Ain KB, Mori Y, Refetoff S. Reduced clearance rate of thyroxine-binding globulin (TBG) with increased sialylation: a mechanism for estrogen-induced elevation of serum TBG concentration. J Clin Endocrinol Metab 1987;65:689-96.
Insulin requirement after one year of insulin therapy in type 2 diabetic patients dependent on fasting C-peptide

Dear Editor,

The aim of our study was to evaluate any relationship between fasting C-peptide level and insulin requirement in newly insulin-treated type 2 diabetic patients with sulphonylurea failure. Additionally, we determined the predictive value of C-peptide as a parameter for insulin requirement. A total of 110 patients with secondary failure of sulphonylurea were investigated.

Patients were divided into four groups: patients with C-peptide <1.0 ng/ml (n=16), 1.0 to 1.9 ng/ml (n=44), 2.0 to 3.4 ng/ml (n=36) and ≥3.5 ng/ml (n=14) as groups with low, normal, moderately high and very high peptide.

We measured insulin requirement, fasting blood glucose (FBG), HbA1c and body weight at the beginning of insulin therapy and one year later. In addition, the C-peptide/FBG quotient was calculated in all patient groups.

Patients with higher C-peptide showed a higher body weight, the difference was significant (p<0.01). At the beginning as well as at the end of the study, insulin requirement was greater in the group with low C-peptide after adjustment for the body weight.

The insulin requirement was IU/kg/day 0.52 ± 0.21 in the low C-peptide group and 0.37 ± 0.15 in patients with normal C-peptide (p<0.01) as can be seen in figure 1. HbA1c decreased similarly (1.5 to 1.8%) and the gain in body weight was also the same in each group (on average 2.5%). All the data are summarised in table 1. The ratio of C-peptide/FBG <0.01 was the most sensitive predictor for

<table>
<thead>
<tr>
<th>C-peptide</th>
<th>&lt;1.0 ng/ml</th>
<th>1.0-1.9 ng/ml</th>
<th>2.0-3.4 ng/ml</th>
<th>≥3.5 ng/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>73 ± 154</td>
<td>76 ± 12</td>
<td>78 ± 14</td>
<td>95 ± 17</td>
</tr>
<tr>
<td>Gain in body weight (%)</td>
<td>2.8</td>
<td>2.9</td>
<td>2.5</td>
<td>2.3</td>
</tr>
<tr>
<td>HbA1c (g)</td>
<td>7.9 ± 1.2</td>
<td>7.8 ± 1.2</td>
<td>8.1 ± 1.1</td>
<td>7.9 ± 1.4</td>
</tr>
<tr>
<td>Decrease (%)</td>
<td>1.7</td>
<td>1.8</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>188 ± 82</td>
<td>198 ± 99</td>
<td>202 ± 102</td>
<td>212 ± 96</td>
</tr>
<tr>
<td>Decrease (%)</td>
<td>11.3</td>
<td>20.1</td>
<td>16.5</td>
<td>19.1</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>199 ± 56</td>
<td>202 ± 64</td>
<td>204 ± 69</td>
<td>199 ± 54</td>
</tr>
<tr>
<td>Decrease (%)</td>
<td>6.8</td>
<td>9.8</td>
<td>12</td>
<td>13.1</td>
</tr>
<tr>
<td>Insulin dose (IU/day)</td>
<td>38 ± 16</td>
<td>28 ± 12</td>
<td>31 ± 15</td>
<td>37 ± 15</td>
</tr>
<tr>
<td>Increase (%)</td>
<td>11.7</td>
<td>8.4</td>
<td>6.4</td>
<td>8.3</td>
</tr>
<tr>
<td>Insulin dose (IU/kg/day)</td>
<td>0.52 ± 0.21</td>
<td>0.37 ± 0.15</td>
<td>0.40 ± 0.17</td>
<td>0.40 ± 0.13</td>
</tr>
<tr>
<td>Increase (%)</td>
<td>8.3</td>
<td>2.7</td>
<td>5.2</td>
<td>7.5</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.002.
insulin requirement in the groups with low and normal C-peptide (100 and 93%, respectively), but not in patients with higher C-peptide (67 and 21% respectively).

In earlier years, basal as well as stimulated C-peptide (after glucagon stimulation) were used as an indicator for insulin requirement in type 2 diabetic patients undergoing oral antidiabetic therapy. In several studies it has been shown that low C-peptide concentrations demonstrate insulin deficiency, and high concentrations insulin resistance. The relation between fasting C-peptide and fasting blood sugar has been described as a more potent marker for insulin dependency. In our study a ratio of C-peptide/NBG <0.01 was found in all patients with low and in nearly all subjects with normal C-peptide. Thus, this quotient was only a potent predictor for insulin requirement in patients with low and normal C-peptide (<2.0 ng/ml).

In summary, insulin requirement was significantly higher in the low C-peptide group, though the body weight increases with the rising C-peptide levels. The ratio C-peptide/FBG <0.01 has a predictive potency only in patients with low and normal C-peptide.

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REFERENCES


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Dear Editor,

In their otherwise excellent review of familial Mediterranean fever (FMF), Lidar and Livneh argue against testing for Mediterranean fever gene (MEFV) mutations both in their diagnostic algorithm and in their subsequent discussion of the case. Although the clinical criteria for FMF are highly sensitive and specific, incorporation of genetic testing will not only confirm the diagnosis but adds valuable information about prognosis as the frequency of secondary amyloidosis varies between genotypes. Moreover, identifying the MEFV mutations in affected cases is crucial if genetic testing is to be offered to other family members. The FMF phenotype can show considerable intrafamilial variation and siblings of affected cases could be asymptomatic but still develop amyloidosis (type II FMF) which is potentially avoidable if treatment is instigated in a timely manner. Finally, mutation analysis for the common FMF mutations is inexpensive and readily available. For these reasons genetic testing should be an integral part of the diagnostic work-up of suspected cases, even when the clinical picture is obvious.

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Department of Medical Genetics, Jewish General Hospital, A802, 3755 Cote St Catherine, Montreal Quebec H2T 1E2, Canada, e-mail: marc.tischkowitz@mcgill.ca

REFERENCES

Dear Editor,

We agree with Dr Tischkowitz's comment regarding the importance of MEFV mutation analysis in assessing the prognosis of a patient with FMF. The presence of the M694V genotype has indeed been associated with a phenotypically more severe disease as well as an increased risk of developing amyloidosis. We also affirm Dr Tischkowitz's contention that identification of this genotype should prompt screening of family members for the presence of asymptomatic amyloidosis (phenotype II). Our difference of opinion, therefore, is merely semantic. While we do not routinely recommend MEFV mutation analysis in the diagnostic work-up of a patient, as the finding of one, two or null mutations will not add or distract from the clinical diagnosis when the patient fulfills the Tel-Hashomer criteria, we do propose genetic testing, a priori, in clinically equivocal cases in which identification of two MEFV mutations serves to confirm the diagnosis of FMF. We also believe that mutation analysis has an important role in the prognostic work-up of a clinically diagnosed patient, for the reasons mentioned above.

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Heller Institute of Medical Research, Sheba Medical Center, Israel, *corresponding author: e-mail: merav.lidar@sheba.health.gov.il

REFERENCE
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The Netherlands Journal of Medicine publishes papers in all relevant fields of internal medicine. In addition to reports of original clinical and experimental studies, reviews on topics of interest or importance, case reports, book reviews and letters to the editor are welcomed.

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The language of the Journal is English. English idiom and spelling is used in accordance with the Oxford dictionary. Thus: Centre and not Center, Tumour and not Tumor, Haematology and not Hematology.

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**CASE REPORT**

A 41-year-old female presented to our department with a three-week history of fever, and painful and tender swelling in the right side of her neck. After several cycles of antibiotherapy no improvement was observed.

On admission, her general condition was good, with an axillary temperature of 38°C, which usually increased at night. On physical examination, she had multiple and tender lymphadenopathies located in the right upper and middle jugular chain and posterior triangle of the neck; the largest was 2 x 2 cm in diameter. Physical examination revealed no other abnormalities.

Laboratory studies showed no abnormalities. A purified protein derivative (PPD) test was negative. Blood, urine, and throat cultures grew no organisms. Serology titres for Ebstein-Barr virus, cytomegalovirus, herpes simplex virus, *Toxoplasma*, *Rubella* and *Brucella* were negative. A cervical magnetic resonance imaging (MRI) scan demonstrated multiple lymphadenopathies which were 1.5 x 2 cm in diameter in the right upper and lower anterior cervical region and posterior cervical region (figure 1).

Due to the persistence of fever and swelling for three weeks, a fine-needle aspiration cytology was performed. Cytological features suggested a reactive lymphadenitis, but a proliferative disease could not be excluded. Thus, an excisional biopsy was performed, with removal of one of the enlarged cervical nodes. Histopathological examination of cervical lymph node biopsy disclosed necrotic areas, histiocytic accumulation, lymphocyte and immunoblast infiltration. Immunohistochemical study showed positive staining for CD68 on histiocytes (figure 2).

**WHAT IS YOUR DIAGNOSIS?**

See page 263 for the answer to this photo quiz.

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**PHOTO QUIZ**

An unusual cause of cervical lymphadenopathies

M. Sagit*, I. Akin, B.O. Elverici, C. Yurdakul

Departments of ¹ENT and ²Pathology, Diskapi Yıldırım Beyazıt Training and Research Hospital, Yakacık Mahallesi Bulut Sokak No:40/13, Keçiören- Ankara 06310, Turkey, *corresponding author: tel.: +90 312359 38 83, fax: +90 312318 66 90, e-mail: musagit@yahoo.com

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**Figure 1.** Ti sagital section of the MRI showing multiple lymphadenopathies in the right posterior cervical region

**Figure 2.** Immunohistochemical study shows positive CD68 staining on histiocytes (DAB Chromogen 400 x)
DIAGNOSIS

Based upon these histopathological findings, the diagnosis of Kikuchi-Fujimoto histiocytic necrotising lymphadenitis was made. There are no definite laboratory tests available for the diagnosis of Kikuchi-Fujimoto disease (KFD). Definitive diagnosis of KFD can only be made on direct histopathological examination of a lymph node biopsy. The typical histopathological features of the KFD include lymph node necrosis with karyorrhexis surrounded by histiocytes, without granuloma, neutrophil or plasma cell infiltration.\(^1\)

Its recognition is crucial, especially because this disease can be mistaken for systemic lupus erythematosus and malignant lymphoma.\(^2\)

There is no radiographic finding specific for KFD. Computed tomography and MRI do not yield features that distinguish KFD from other diseases which commonly involve lymph nodes such as lymphoma, tumour metastases, or tuberculosis.\(^3\)

The characteristic clinical presentation is cervical lymphadenopathy, which is often painful or tender on palpation. Occasionally the sole symptom of the disease is a fever of unknown origin without other associated clinical features. Additional complaints include nausea, diarrhoea, headache, dermatological lesions and constitutional disturbances.\(^2\)

There is no specific treatment for KFD, analgesics-antipyretics, nonsteroidal anti-inflammatory drugs and corticosteroids may be used to relieve distressing local and systemic complaints. Spontaneous recovery occurs in one to four months. However, a small percentage of cases may have a recurrence within a few weeks from the first event and relapses have been described many years after the initial episode.\(^4\)

Together with the high risk for development of an autoimmune disease or malignancy such as lymphoma, these characteristics mean that long-term follow-up is mandatory for these patients.

Cervical lymph node enlargement with a prolonged fever requires a careful differential diagnosis which should include the possibility of KFD.

REFERENCES


Skin lesions as a first presentation

A.J.G. Jansen¹, M.B.L. Leijs², H.F.G.M. van den Ingh³, T.T. Tio⁴*

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CASE REPORT

A healthy 79-year-old man presented to the Department of Dermatology in September 2003 with purple-red, swollen lesions involving the whole body for a period of five weeks (figure 1). The eyebrows of the right eye were swollen, the upper more than the lower. At that time laboratory results were: haemoglobin 7.2 mmol/l, platelet count 162 x 10⁹/l, white blood cell count 6.9 x 10⁹/l with a monocytosis of 20.9% and C-reactive protein of 255 mg/l. Skin biopsy is shown in figure 2.

WHAT IS YOUR DIAGNOSIS?

See page 265 for the answer to this photo quiz.

Figure 1A. Cutaneous lesions

Figure 1B. Cutaneous lesions on right shoulder

Figure 2. Skin biopsy, CD68 colouring: 20 x

Pictures made after starting treatment, but hardly changed compared with moment of presentation.
DIAGNOSIS

Bone marrow aspiration showed a hypercellular bone marrow with an increase of atypical myeloid blasts. The skin and bone marrow biopsies were negative for CD79a, CD20, CD3 and S-100 and positive for Lysozyme, CD43, CD13 and CD68. The diagnosis of chronic myelomonocytic leukaemia (CMML) was made and he was treated with etoposide 50 mg daily. Due to toxicity, the etoposide treatment had to be stopped and the patient died in November 2003 of respiratory insufficiency.

CMML is a haematological malignancy characterised by a wide heterogeneity of clinical presentations and course of disease. In 2001 the World Health Organisation (WHO) re-classified acute myeloid leukaemia (AML), including myelodysplastic syndrome (MDS), chronic myeloproliferative disease (CMPD) and the myelodysplastic/myeloproliferative (MDS/MPD) clonal haematopoietic stem cell diseases. The features of MDS/MPD overlap with those of MDS and CMPD, and CMML was re-classified into MDS/MPD by the WHO. The incidence of CMML is 0.46/100,000. The natural course of CMML is variable, with a median three-year survival of 29%. The most common presenting symptoms in CMML are caused by bone marrow dysfunction and the resultant peripheral blood cytopenia. CMML has been associated with various dermatological conditions, but rarely involves the skin directly. Skin involvement is often a late stage of the disease. The clinical appearance of leukaemia cutis is highly variable and described as an erythematous maculopapular rash, numerous widespread skin nodules of less than 1 mm in diameter, an unusual localised bullous lesion, and a widespread itchy rash. The most important treatment for CMML is systemic chemotherapy. For cutaneous lesions, however, the addition of whole-body electron-beam irradiation followed by consolidation chemotherapy may be advised.

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