Ulcerated nodules of the tongue; what is your diagnosis?

Pitfalls in cytokine measurements

Management of *S. aureus* bacteremia

Ticking off diagnoses of abdominal pain

Subacute renal injury in hypothyroidism

Hemothorax: a complication of hernia
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Contents

EDITORIAL

Negative results worth publishing 309
P.L.A. van Daele

ORIGINAL ARTICLES

Pitfalls in cytokine measurements – Plasma TGF-β1 in chronic fatigue syndrome 310

Occurrence and management of an aberrant free T4 in combination with a normal TSH 314
K.M. van Veggel, J.M. Rondeel, S. Anten

Management of S. aureus bacteraemia in the Netherlands; infectious diseases consultation improves outcome 322
M. Cobussen, F.H. van Tiel, A.M.L. Oude Lashof

CASE REPORTS

Coronary artery spasms due to tyrosine kinase inhibitors used in chronic myeloid leukemia 330

Ticking off diagnoses of abdominal pain: early neuroborreliosis with radiculopathy 336
J.M. Stolk, C. van Nieuwkoop, M.P.J.A. van der Voorn, S. van Erp, N.D. van Burgel

Subacute renal injury in hypothyroidism: a case report of an unusual phenomenon 339
D.M. van Velzen, Y.H. Krul-Poel, M. den Heijer, S. Simsek

PHOTO QUIZZES

Hemothorax: a very rare complication of late diaphragmatic hernia 343
Ting-Cheng Wang, Chin-Wang Hsu, Yuan-Pin Hsu

Swelling of the breast after cosmetic augmentation 345
W. van ’t Hart, A.J.G. Jansen, K.H. Lam, P.J. Lugtenburg, D. Vasilic

Ulcerated nodules of the tongue 347
S. Capodiferro, E. Maiorano, A. Tempesta, L. Limongelli, G. Favia

LETTER

Q fever: hospitalisation and other concerns 349
V.M. dos Santos

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Negative results worth publishing

P.L.A. van Daele

Many patients in my out-patient clinic have one symptom in common: they are tired. If I know their diagnosis I tend to link their tiredness to the underlying disease and hope that treatment will lessen their fatigue. I get disappointed a lot, fatigue is a symptom that is hard to treat. This is especially true for patients presenting with fatigue whom I can’t diagnose. Some of these I ultimately diagnose as suffering from chronic fatigue syndrome (CFS), a long-lasting condition characterized by intense and disproportional fatigue after exertions, frequently accompanied by musculoskeletal pain, headaches, cognitive impairments and other symptoms. It is a syndrome with major impact on the quality of life. It is commonly believed that CFS is due to low grade inflammation and that inhibition of inflammation may therefore lead to alleviation of symptoms. But where is the evidence? There are numerous studies on gene expression profiles and cytokine levels, as well as on numbers and types of T- and B-cells that report differences between patients and healthy, non-fatigued controls. Unfortunately, however, the results of such studies are highly inconsistent. There is also a tendency to report positive results from studies while rejecting negative results, so that the effects of alterations in immune-regulation may be overestimated. It is hardly surprising, therefore, that no immune-modulating treatment has so far unequivocally led to major improvements or to total resolution of symptoms in patients with CFS.

In the current issue of the journal Roerink et al. report on the results of their study on TGF-beta in patients with CFS. In a nutshell: they find no evidence for a major role of TGF-beta in CFS, or at least no difference in circulating levels between patients and controls. Apart from presenting negative results the authors also hint on reasons for discrepancies between previous studies on this subject, pointing at methodological pitfalls in laboratory analyses. An issue often overlooked but highly important. That said, the pathophysiologic puzzle in CFS remains unsolved.

REFERENCES

Pitfalls in cytokine measurements – Plasma TGF-β1 in chronic fatigue syndrome

M.E. Roerink1*, M.E. van der Schaaf2,3, L.J.A.C. Hawinkels4, R.P.H. Raijmakers1, H. Knoop2,5, L.A.B. Joosten1, J.W.M. van der Meer1

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ABSTRACT

Background: Serum TGF-β1 concentrations are reported to be elevated in chronic fatigue syndrome (CFS). However, measurement of circulating cytokines is a complex procedure and control of pre-analytical procedures is essential. The objective of the current study was to measure circulating TGF-β1 concentrations in CFS patients compared to healthy controls, taking into account differences in pre-analytical procedures.

Methods: Two cohorts of female CFS patients were included. In both studies patients were asked to bring a healthy, age-matched control. At baseline, TGF-β1 levels were measured in plasma and additionally P-selectin, a marker of platelet activity, was determined in a subgroup of participants.

Results: 50 patients and 48 controls were included in cohort I, and 90 patients and 29 controls in cohort II. Within the cohorts there were no differences in TGF-β1 concentrations. However, between the cohorts there was a large discrepancy, which appeared to be caused by differences in g-force of the centrifuges used. The lower g-force used in cohort II (1361 g) caused more platelet activation, reflected by higher p-selectin concentrations, compared to cohort I (p < 0.0001), which was confirmed in a second independent experiment. There was a correlation between TGF-β1 and p-selectin concentrations (r 0.79, p < 0.0001).

Conclusion: These results demonstrate that control of pre-analytical procedures is an essential aspect when measuring circulating cytokines. No evidence for enhanced TGF-β1 in patients with CFS was found.

KEYWORDS

Chronic fatigue syndrome, TGF-β1, platelets

INTRODUCTION

Chronic fatigue syndrome (CFS) is an enigmatic disorder, in which patients suffer from incapacitating fatigue, pain and a series of associated symptoms. The complaints are not due to any known underlying disease, and the pathophysiology has not been elucidated. CFS may be provoked by infections such as infectious mononucleosis, or by any of a series of other triggers. Because of the association with preceding infection and the similarities in symptomatology with sickness behaviour that can be induced by proinflammatory cytokines, many studies aiming to find abnormal cytokine regulation have been performed on CFS. The picture that emerges from these studies is by no means consistent. In publications the reasons for the discrepancies found often remain unclear, but it seems likely that factors like age and gender of the patients, composition of the control groups, the robustness of the pre-analytical procedures (such as sampling, handling, centrifugation and storage) and the kind of assays used, play an important role. In a recent systematic review on cytokines in CFS, the most consistent finding was elevation of the anti-inflammatory cytokine transforming growth factor β (TGF-β).

Recently we performed a large prospective cytokine study in female CFS patients. This study was methodologically robust, as the age- and gender-matched controls from...
All samples were acid activated to TGF-β1, age did not differ significantly. The study was conducted at the Department of Internal Medicine and Expert Centre for Chronic Fatigue (ECCF) of the RadboudUMC, Nijmegen, the Netherlands. Details of the study were described elsewhere. In another cohort of CFS patients and similarly matched controls, we also sampled blood to measure inflammatory markers. In the present report we demonstrate the relevance of stringent methods of controlling for variability that may arise during the pre-analytical phase. To this end we describe the results of TGF-β1 measurements in these two CFS cohorts.

MATERIALS AND METHODS

Patients
Two cohorts of patients with CFS were enrolled in this study. The first cohort (cohort I) consisted of patients who participated in a double-blind randomized controlled trial (RCT) on the effect of IL-1 inhibition on CFS-related symptoms. The study was conducted at the Department of Internal Medicine and Expert Centre for Chronic Fatigue (ECCF) of the RadboudUMC, Nijmegen, the Netherlands. Details of the study were described elsewhere. In short, 50 female patients aged between 18 and 59 were enrolled, who fulfilled the Center for Disease Control (CDC) criteria for CFS. Use of medication was not allowed, oral contraceptives and paracetamol excepted. Each of the patients was asked to bring a healthy female neighborhood control in her own age range (± 5 years), to their first study visit. The second cohort (cohort II) consisted of 90 female patients between 18 and 65 years fulfilling the CDC criteria for CFS. The criteria for inclusion and exclusion have been described in detail elsewhere. Just as with Cohort I, a proportion of patients was asked to bring a healthy female neighborhood control matched for age and gender to their first study visit. All participants provided written and oral informed consent before inclusion. The hospitals’ ethics committee (Commissie Mensgebonden Onderzoek Regio Arnhem/Nijmegen) approved the study protocols (2014/025 and 2013/113). The study was performed in accordance with the declaration of Helsinki.

Questionnaires
Fatigue was measured in both patients and controls using the fatigue severity subscale of the checklist individual strength (CIS), which has been used frequently with CFS patients. Scores on the CIS-f run from 8 to 56, a score ≥ 35 reflecting severe fatigue.

Blood collection
Blood samples were collected at baseline at the outpatient clinic for Internal Medicine at the RadboudUMC in Nijmegen, the Netherlands from all patients of Cohort I. Samples of controls were collected simultaneously with those of patients. Venous blood was collected in EDTA tubes, and kept on ice until centrifugation, which was performed within 2-3 hours (±59 g). Plasma aliquots were then kept frozen at -80°C for maximally 2 years. For Cohort II, the sampling, handling (centrifugation speed 1361 g) and storage of the blood of patients and controls were done in similar fashion at the Donders Centre for Neuroimaging in Nijmegen, the Netherlands.

Measurements of TGF-β1 and P-selectin
Total TGF-β1 levels were measured by enzyme-linked immunosorbent assay (ELISA), as previously described in detail (R&D systems). All samples were acid activated to activate latent TGF-β1 (1 M hydrochloric acid, 30 min, room temperature, neutralization with 1M NaOH, followed by direct analysis). All assays were performed on the same day using the same reagents. P-selectin was measured in a proportion of samples by ELISA (R&D systems) according to the instructions of the manufacturer.

Confirmation experiment
For a second experiment, two EDTA venous blood samples were taken from 5 healthy controls at the same time point. Samples were handled in similar fashion, the only difference being the g-force used for plasma centrifugation. One sample from each participant was centrifugated at a speed of ±59 g and one at 1361 g. Subsequently platelet numbers were measured in all samples.

Statistical analysis
Study data were analyzed using IBM SPSS statistic package version 22. All continuous variables are presented as means and standard deviations (SD)/ standard error of the mean (SEM). For group comparison a Students T-test was used. Pearson’s correlation was used for the correlation between TGF-β1 and P-selectin.

RESULTS

Baseline characteristics
As displayed in table 1, age did not differ significantly between patients and controls of both groups. As expected, patients had higher fatigue scores compared to controls (51.5 vs 19.1, p < 0.001), but there were no differences between cohort I and II.

TGF-β1 and P-selectin
The results of the TGF-β1 measurements in the patients and controls from Cohort I are depicted in figure 1A. No differences in TGF-β1 concentrations were found...
between patients and healthy controls. Likewise, the results of the measurements in Cohort II did not reveal differences between CFS patients and controls (figure 1B). However, there was a large differences in the TGF-β1 concentrations found between Cohort I and Cohort II. As it is known that platelets are a rich source of TGF-β1, we wondered whether the higher TGF-β1 levels could be caused by a higher number of (activated) platelets in Cohort 2. To explore whether platelet activation differed between the two groups, we measured P-selectin as a platelet marker in a random selection of samples. The concentration of P-selectin differed greatly between the two cohorts (p < 0.001; figure 2). There was a strong correlation (r 0.79, p < 0.0001) between the concentrations of TGF-β1 and P-selectin. Differences in platelet activation could be explained by differences in the g-force of the centrifuges used at the two study locations.

Confirmation experiment
Platelet counts were significantly lower in the samples centrifugated at the highest g-force of 2959 g (4.4 ± 0.5 x 10^3/μl vs. 132.2 ± 16.45 x 10^3/μl, p < 0.001).

Table 1. Baseline characteristics of chronic fatigue syndrome patients and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Cohort I</th>
<th>Cohort II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CFS (n = 50)</td>
<td>HC (n = 48)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>31 (10)</td>
<td>31 (10)</td>
</tr>
<tr>
<td>Fatigue severity (CIS-f)</td>
<td>52 (4)</td>
<td>20 (11)</td>
</tr>
</tbody>
</table>

* (): standard deviation
**DISCUSSION**

In this report we demonstrate that even with scrupulous methodology, inaccurate results may be obtained. It turned out that the different properties of the centrifuges used at the two study locations were responsible for differences in platelet numbers and platelet activation (as assessed by P-selectin measurements).

Although it is well known that platelets contain considerable amounts of TGF-β1,14-16 this is often not taken into account when measuring circulating concentrations of this cytokine. Many cytokine studies do not adequately describe the pre-analytical procedures of patient samples and controls.

In a recent study on TGF-β1 in CFS patients a pitfall similar to the one in the present paper was encountered. In this otherwise carefully performed study differences in the duration of centrifugation between two technicians explained the differences found in TGF-β1 between patients and controls.13 Our current data show that if, for example, samples of the controls of cohort I would have been prepared like those of cohort II, strong differences could have been observed, which would not have been due to actual differences caused by the underlying disease but solely to sample handling.

The use of different sample collections for patients and controls is fairly common. This was in fact the case in the studies that incriminated the retroviruses XMRV and XMLV.14-15 It led to results that misled both the scientific community and more sadly, the patients suffering from CFS.16

In conclusion, we want to make a plea for better standardization of pre-analytical sample handling for patient studies, not only in CFS research. The use of neighborhood controls who are bled at the same time and location, whose samples undergo the exact same procedure as those of the patients, is a good way of enhancing the quality of such research. In addition, precise reporting on the nature of the control group and the pre-analytical procedures followed with controls and patients is essential.

**ACKNOWLEDGEMENTS**

The authors thank P. ten Dijke for his suggestions with respect to TGF-β1 analysis and C. de Bree for her help with the P-selectin analysis.

This study was supported by the Dutch CFS/ME patient advocacy group and an independent donor that wishes to remain anonymous. The funders had no role in study design, data collection, data analysis, data interpretation or writing of the report.

J. van der Meer, H. Knoop, L. Joosten and M. Roerink defined the research theme and designed the research methods. M. Roerink, L. Hawinkels, R. Raijmakers and M. van der Schaaf conducted the study and analysed the data. M. Roerink interpreted the results and wrote the first draft of the manuscript; the other authors reviewed and edited the manuscript.

**DISCLOSURES**

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

**REFERENCES**

Occurrence and management of an aberrant free T4 in combination with a normal TSH

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ABSTRACT

Background: Thyroid function tests may show the combination of a normal concentration of serum thyroid-stimulating hormone (TSH) and an increased or decreased level of free thyroxine (free T4). How often this occurs is unclear and not everyone is familiar with how it should be addressed.

Methods: We conducted a retrospective cohort study of all adult patients who presented at a non-academic general hospital in the Netherlands between 1 January 2010 and 31 December 2014 and yielded an increased or decreased free T4 in combination with a normal TSH. Exclusion criteria included the use of thyroid medication, pregnancy, a history of thyroid surgery and treatment with radioactive iodine. The medical records of the patients included were retrieved and evaluated.

Results: Of the 30,143 combined TSH and free T4 measurements in 23,199 individual patients, 1005 measurements (3.33%) in 775 patients (3.34%) yielded an aberrant free T4 in combination with a normal TSH. 398 patients (1.72%) had a persistent aberrant free T4, 349 (87.7%) of whom had a decreased free T4 and 49 (12.3%) an increased free T4. In 58 of the 398 patients (14.6%) with a persistent aberrant free T4 a possible cause was established by the treating physician. However, upon re-examination of medical files a possible causative factor could be identified in 123 patients (30.9%).

Conclusion: In our study population the prevalence of hyperthyroxinemia or hypothyroxinemia in combination with a normal TSH was 334 per 10,000 patients. When records were thoroughly searched, identification of potential causative factors increased substantially. Clinicians should be encouraged to check for underlying causes.

KEYWORDS

Free thyroxine, thyroid, thyroid dysfunction, thyroid-stimulating hormone

INTRODUCTION

Thyroid function tests may show a combination of a normal concentration of serum thyroid-stimulating hormone (TSH) and an increased or decreased concentration of serum free thyroxine (free T4). Often hyperthyroxinemia or hypothyroxinemia in combination with a normal TSH has limited clinical relevance, for example when it is caused by changes in T4-protein binding due to certain medication. On the other hand, a normal TSH and aberrant free T4 can reflect a serious underlying condition such as a pituitary disorder.

The current literature is unclear about the frequency of the occurrence of hyperthyroxinemia and hypothyroxinemia in combination with a normal TSH and there is discussion about how it should be addressed. Follow-up can possibly be improved when physicians have more knowledge about its probable causes in every day practice.

The aim of this study was to determine the 5 year prevalence of a normal TSH in combination with an aberrant free T4. Furthermore, this study tried to determine whether any causative factors could be established by the treating physician and whether the treating physician ordered any further diagnostic tests or initiated any treatment. We also checked the medical files ourselves for any identifiable factors, even if no cause was recorded by the treating physician.

Table 1 gives an overview of the many medications and conditions that can cause the combination of hyperthyroxinemia or hypothyroxinemia and a normal TSH.
**Van Veggel et al. Occurrence of an aberrant free T4 with a normal TSH.**

**Materials and Methods**

**Study design and settings**
A retrospective cohort study was performed at Alrijne Hospital, Leiderdorp, the Netherlands, a non-university general hospital situated in an urban area. Alrijne Hospital has 440 staffed beds, 18,000-20,000 admitted patients per year and around 126,000 new outpatient visits per year.

**Patients**
Eligibility criteria included all patients aged 18 years and older who were seen by any kind of medical specialty as either an in- or outpatient, between 1 January 2010 and 31 December 2014. Patients were included if laboratory results showed an aberrant free T4 in combination with a normal TSH. Patients were excluded if they used thyroid hormone replacement (for example levothyroxine and liothyronine), had undergone thyroid surgery or had been treated with radioactive iodine in the last 2 months, and if they were pregnant. Patients without any notes in their medical file were excluded as well.

**Assays**
Prior to 13 May 2014 concentrations of free T4 and TSH were determined by a Siemens Immulite 1000 immuno-assay analyser. Maximal total coefficients of variation for free T4 and TSH were 12.1% and 17.5%. Reference values of free T4 and TSH were 10.3-24.5 pmol/l and 0.4-4.0 mU/l. As of 13 May 2014 the laboratory used a chemiluminescent microparticle immunoassay (CMIA; Architect, Abbott Diagnostics USA). The Abbot assay has a dilution factor of 75 before measuring FT4. Maximal total coefficients of variation were 7.8% and 5.3% for free T4 and TSH respectively. Reference values of free T4 and TSH were 10-19 pmol/l and 0.27-4.2 mU/l, respectively. Concentrations outside the reference range were considered abnormal.

**Data collecting**
The institution’s computerized laboratory information system was used to identify all patients with a normal TSH in combination with an aberrant free T4 and to evaluate their medical records for general data, such as age at which the aberrant value was determined, sex, length, weight, body mass index, TSH, free T4, free T3, total T4, total T3, anti-thyroid peroxidase antibodies (anti-TPO), anti-thyroglobulin antibodies (anti-TG) and anti-TSH-receptor (anti-TSH-R). We evaluated recorded causes of hyperthyroxinemia and hypothyroxinemia in combination with a normal TSH and looked into whether the treating physician ordered any tests to examine possible causes. We also checked ourselves if we could identify a cause for the aberrant combinations of free T4 and TSH, even if no cause was recorded by the treating physician. Furthermore we determined if the treating physician started treatment or arranged for some other follow-up.

**Medical Ethical Committee**
The Medical Ethical Committee of Alrijne Hospital granted permission to perform a medical record study.

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**Table 1. Causes of hypothyroxinemia and hyperthyroxinemia in combination with a normal TSH and corresponding data that have been evaluated in patients’ medical records**

<table>
<thead>
<tr>
<th>Causes of a normal TSH in combination with a decreased free T4</th>
<th>Causes of a normal TSH in combination with an increased free T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased concentrations of TBG: hepatitis, porphyria, estrogen, heroin, methadone, mitotane, 5-fluorouracil, selective estrogen receptor modulators (e.g. tamoxifen, raloxifene), perphenazine</td>
<td>Decreased concentrations of TBG: liver failure, nephrotic syndrome, androgens, anabolic steroids, glucocorticoids, nicotinic acid, L-asparaginase</td>
</tr>
<tr>
<td>Increased clearance of thyroxine therapy: phenobarbital, primidone, phenytoin, carbamazepine, oxcarbazepine, rifampicin, growth hormone, sertraline, tyrosine kinase inhibitors (e.g. imatinib, sunitinib), quetiapine, stavudine, nevirapine</td>
<td>Inhibition of T4 binding to TBG: salicylates, furosemide, free fatty acids, phenytoin, carbamazepine, non-steroidal anti-inflammatory drugs, heparin</td>
</tr>
<tr>
<td>Decreased release of thyroid hormone by the thyroid: lithium</td>
<td>Inhibition of thyroid hormone transport through the plasma membrane: amiodarone</td>
</tr>
<tr>
<td>Critical illness</td>
<td>Critical illness</td>
</tr>
<tr>
<td>Central hypothyroidism: decreased pituitary function due to pituitary adenomas, compressive lesions, cranial surgery or irradiation, empty sella, auto-immune disease, vascular accidents, infiltrative lesions (e.g. hemochromatosis), infections (e.g. tuberculosis), inherited disease</td>
<td>Pituitary TSH adenoma (e.g. TSHoma)</td>
</tr>
<tr>
<td>Thyroid hormone resistance</td>
<td>Thyroid hormone resistance</td>
</tr>
</tbody>
</table>

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

Using the exclusion criteria, out of a total of 775 patients 271 patients (35%) were excluded from this study and 504 patients (65%) were included.

During the 5-year study period, 37,331 TSH tests were performed in 30,143 cases, of which free T4 was measured as well, reflecting 23,199 individual patients. The combination of a normal TSH with an aberrant free T4 was identified 1005 times in 775 individuals (prevalence 334 per 10,000).
Van Veggel et al. Occurrence of an aberrant free T4 with a normal TSH.

Table 2. Patient characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (range)</th>
<th>Number of patients</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>58 (18-90)</td>
<td>389 (61.3 %)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>309 (61.3 %)</td>
<td></td>
</tr>
<tr>
<td>TSH in mU/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time period 1</td>
<td>Number of patients</td>
<td>432 (92.8 %)</td>
<td>9.7 (5.5-10.2)</td>
</tr>
<tr>
<td></td>
<td>Number of patients</td>
<td>72 (17.2 %)</td>
<td>44 (61.1 %)</td>
</tr>
<tr>
<td>Time period 2</td>
<td>Number of patients</td>
<td>44 (61.1 %)</td>
<td>9.6 (6.9-9.9)</td>
</tr>
<tr>
<td></td>
<td>Number of patients</td>
<td>28 (38.9 %)</td>
<td>28 (38.9 %)</td>
</tr>
<tr>
<td>Free T4 in pmol/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time period 1</td>
<td>Number of patients</td>
<td>401 (92.8 %)</td>
<td>9.7 (5.5-10.2)</td>
</tr>
<tr>
<td>Decreased free T4 (&lt; 10.3)</td>
<td>Number of patients</td>
<td>31 (7.2 %)</td>
<td>26.6 (24.6-37.9)</td>
</tr>
<tr>
<td>Increased free T4 (&gt; 24.5)</td>
<td>Number of patients</td>
<td>44 (61.1 %)</td>
<td>44 (61.1 %)</td>
</tr>
<tr>
<td>Time period 2</td>
<td>Number of patients</td>
<td>28 (38.9 %)</td>
<td>28 (38.9 %)</td>
</tr>
<tr>
<td>Decreased free T4 (&lt; 10.0)</td>
<td>Number of patients</td>
<td>19.9 (19.1-38.4)</td>
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<tr>
<td>Increased free T4 (&gt; 19.0)</td>
<td>Number of patients</td>
<td>19.9 (19.1-38.4)</td>
<td></td>
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<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical patients</td>
<td>36 (11.1 %)</td>
<td>36 (11.1 %)</td>
<td></td>
</tr>
<tr>
<td>Outpatient clinic</td>
<td>448 (88.9 %)</td>
<td>448 (88.9 %)</td>
<td></td>
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</tbody>
</table>

Descriptive characteristics of the study population are shown in table 2. In the table we divided the study period into 2 separate time frames: the period when the Siemens Immulite 1000 immuno-assay analyser has been used and the period when the Abbot assay has been used. Most patients were seen by an internist (37.9%) or a cardiologist (32.3%). Of the 504 patients included, 398 had a persistent aberrant free T4. In 106 patients (21%) the aberrant free T4 concentrations did not persist: in 88 patients (83%) free T4 concentrations normalized without any form of intervention, whereas in other patients TSH concentrations became aberrant, also without any intervention. In 349 (87.7%) of the 398 patients with a persistent aberrant free T4, free T4 was decreased in combination with a normal TSH, 49 patients (12.3%) had an increased free T4 in combination with a normal TSH. No explanation for the aberrant values was found in 300 of the 349 patients (86.0%) who had a decreased free T4 in combination with a normal TSH. No additional investigation had been carried out in most of these 300 cases (286 patients, 95.3%) and for none of them thyroid hormone replacement had been prescribed. Additional investigation had been performed for the remaining 14 (4.7%) patients, but no explanation for the aberrant values had been found. Seven (50%) of these patients had been prescribed thyroid hormone replacement. In 49 cases (14%) an explanation for the decreased free T4 in combination with a normal TSH was identified by the treating physician: medication (lithium, amiodarone, venlafaxine, carbamazepine), underweight, a central cause (pituitary adenoma, Sheehan’s syndrome, pituitary hemorrhage, Rathke’s cleft cyst, empty sella, meningioma, hypophysitis), a thyroid related cause (autoimmune hypothyroidism, primary hypothyroidism, goitre, Graves’ disease, thyroid carcinoma, thyroiditis) and assay error. These diagnoses have been described after additional follow-up for 40 of these patients (81.6%). In 81.6% of the 49 patients who had a normal TSH in combination with an increased free T4, no explanation for the aberrant values was found, no additional investigation had been done and none of these patients had received thyroid inhibitory medication. Causes that were found in the remaining patients are: medication (amiodarone), a thyroid related cause (Graves’ disease, toxic nodule) and assay error. Additional investigation had been performed for four (4.4%) of these patients. One (11.1%) of them started on propylthiouracil. In four cases of our study population (one decreased free T4 and three increased free T4) the treating physician sent the patient’s blood to the Erasmus Medical Center Rotterdam to check for an assay error. In all cases an assay error was ‘diagnosed’. The treating physician did not record his considerations in any of these cases. See figure 1 for an overall summary.
Van Veggel et al. Occurrence of an aberrant free T4 with a normal TSH.

### Table 3. Occurrence of known associated factors ('risk factors') for developing an aberrant free T4 concentration in combination with a normal TSH concentration among 504 evaluated patients at baseline

<table>
<thead>
<tr>
<th>Riskfactor</th>
<th>Number of patients with a decreased free T4</th>
<th>Number of patients with an increased free T4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salicylates use</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Amiodarone use</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Furosemide use</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs use</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Free fatty acids</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine use</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids use</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Quetiapine use</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Lithium use</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Androgens use</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Phenytoin use</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Sertraline use</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Selective estrogen receptor modulators use</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine use</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Heparin use</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5-fluorouracil use</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Non-drug factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical illness</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

The ‘other’ group consists of porphyria, liver failure, use of nicotinic acid, heroin, methadone, mitotane, perphenazine, phenobarbital, primodone, rifampicin, tyrosine kinase inhibitors, stavudine, nevirapine, anabolic steroids and L-asparaginase

Next to checking for how many patients the treating physician found a cause for the aberrant values, we also checked the medical files for any identifiable cause of aberrant combinations between free T4 and TSH concentrations. In other words: we looked for ‘risk factors’ a physician can identify by performing an interview and physical examination, and by assessing the medical history and medication usage of the patient, so before any additional investigation has been performed. For 123 of the patients with a persistant aberrant free T4 (30.9%) one or more causal factors for aberrant combinations were identified (table 3).

During data collection we also checked for free T3, total T3 and total T4. Total T3 was measured only in 10 patients (2.0%), free T3 and total T4 were not measured. Anti-TPO, anti-Tg and anti-TSH-R did not contribute to further diagnostic workup.

### DISCUSSION

In our study, screening for thyroid function yielded a combination of a normal TSH and an aberrant free T4 in 3.3% of the patients.

In the current literature various causes of hyperthyroxinemia and hypothyroxinemia in combination with a normal TSH are discussed, as shown in table 1. The most common cause is drug related. For example, anticonvulsants (phenytoin, carbamazepine and phenobarbital) and also rifampicin can increase the metabolic clearance of T4 by enzyme induction. In addition, it has been demonstrated that amiodarone can inhibit the transport through the plasma membrane which can lead to an elevated free T4 in combination with a normal TSH. Other drugs can decrease the binding of T4 to the thyroxine binding globulin (TBG): salicylates, salsalate and certain non-steroidal anti-inflammatory drugs.

It should be stressed that the effect of a drug on protein binding depends on the dilution factor of a sample in a specific assay. An assay with high dilution is less affected by this drug effect. Assay interference may also cause aberrant results. A typical example of assay interference is the inhibitory effect of furosemide on free T4 binding to TBG. In a blood tube this effect continues and this may lead to misleadingly high free T4 concentrations. However, in an assay with a high dilution factor this effect is minimised (see references 9 and 15 for further reading).

In the case of unexpected laboratory results the clinician should always be aware of assay errors and ask the clinical laboratory for further research into this matter.

Another reason why free T4 may be aberrant is critical illness. In cases of critical illness, circulating substances, such as a high serum free fatty acid concentration, can prevent T4 binding to the binding proteins. Also deiodination of thyroid hormones can be affected. This may result in either high or low serum free T4 concentrations. Of the patients included in our study, 9.8% turned out to be critically ill.

A rare but important reason why the TSH may be normal in combination with a decreased free T4 is central (secondary)
hypothyroidism. Since, among other things, this condition can be related to a pituitary adenoma or external compression on the pituitary gland, and might have serious clinical consequences if missed, central hypothyroidism always needs to be considered. We found a central cause in 3.8% of our population. Other possible causes of hyperthyroxinemia and hypothyroxinemia in combination with a normal TSH include abnormal protein binding of TBG, transthyretin and albumin. In familial dysalbuminemic hyperthyroxinemia, for example, binding of T4 to dysalbumin, a structural variant of albumin, is increased. In vivo, this will lead to a high concentration of total T4 and normal free T4 levels. In certain assays, however, this dysalbumin leads to interference and artificially high free T4 concentrations. Certain factors may change binding protein concentrations, and thus may increase or decrease the serum concentrations of T4 and T3. Examples are estrogens, hepatitis and drugs like 5-fluorouracil. We did not find these in our population. Also acute psychosis and reduced thyroxine deiodination can cause hyperthyroxinemia and hypothyroxinemia in combination with a normal TSH. Finally, one should realize that both intra- and interindividual differences in the hypothalamic-pituitary-thyroid axis setpoint are potential causes of aberrant free T4 concentrations.

This study demonstrates that 3.3% of the patients have a combination of a normal TSH with an aberrant free T4 on testing for thyroid function. 87.7% of the included patients had a decreased free T4 in combination with a normal TSH, while an increased free T4 in combination with a normal TSH was less common (12.3%). In most medical files we could not ascertain that additional investigation had been done to find an explanation for the aberrancies. Most of the time we could also not find if the physician recognised this aberrancy: in 81.9% of cases no explanation was found for the aberrancies, and also no additional investigation had been carried out. However, after checking the available medical files we could identify a causal factor in 30.9% of the patients with a persistant aberrant free T4.

Potential explanations for the lack of diagnostic workup in a large proportion of cases included in this study could be unawareness of hyperthyroxinemia and hypothyroxinemia in combination with a normal TSH and its causes, as well as the lack of guidelines regarding its management and the assumption that these conditions most often do not have clinical consequences. This assumption may well be incorrect since recent studies showed that free T4 but not TSH is associated with sudden cardiac death and depression.

**Recommendations for patients with a normal TSH in combination with an aberrant free T4**

Because in 21% of the cases in this study aberrancies were not persistent after the test was repeated, we advise physicians who have patients with this condition to remeasure serum free T4 and TSH after two to three months. In a recent trial a high number of reverted subclinical hypothyroidism was seen in two out of three patients without any therapy upon remeasurement after three months to three years. The time frame of remeasurement in our study was two months to five years. Any easily identifiable causal factor, such as certain medication, should be checked (*tables 1 and 3*), and non-drug related factors such as critical illness, hepatitis and nephrotic syndrome should be evaluated as well.

When hyperthyroxinemia or hypothyroxinemia in combination with a normal TSH is found, the clinical challenge is to recognize a central cause like pituitary adenoma or external compression of the pituitary gland or hypothalamus. Delay of the diagnosis may have serious medical consequences.

One strategy to follow could be that if free T4 persists to be aberrant after repeated measurement in a non-pregnant patient and without any clear explanation (see *table 1 and 3*), one should first consult the laboratory to rule out assay interference. If no assay interference can be established, a central (secondary) cause should be considered. Especially when clinical features suggest thyroid dysregulation, the next step would be either imaging (MRI) of the pituitary gland and hypothalamus or pituitary function tests. Finally, if the aberrancy persists, rare disorders such as thyroid hormone resistance might be considered. This diagnosis may involve identifying a mutation of the thyroid receptor. *Figure 2* shows a flowchart with our suggestions for analysis of hyperthyroxinemia and hypothyroxinemia in combination with a normal TSH.

**Limitations**

This study has several limitations. Incomplete, missing and unreliable information in the medical record may have caused incorrect inclusion or exclusion. This may have caused an incorrect number of explanations given for an aberrant free T4. There is a possibility that the physician did have an explanation for the aberrant free T4, but did not write it down. We only included patients in whom a normal TSH in combination with an aberrant free T4 had been found. In many patients only TSH had been determined and – if normal – no free T4 had been measured. Therefore, the actual number of aberrancies between TSH and free T4 might be much higher. Since drug-induced interference in thyroid function tests is uncommon in assays with a high dilution factor, this fact can be used to identify or rule out true interference. The assay we used in our study had a high dilution factor. Therefore, the true number of drug-induced abnormal tests is probably lower than reported.
CONCLUSION

This study demonstrates that in our population of patients screened for thyroid dysfunction in a non-university general hospital 334 per 10,000 patients had a normal TSH in combination with an aberrant free T4. We also found that many physicians do not follow-up on this condition or record a causative factor. When medical files are searched thoroughly however, identification of a possible causative factor increases from 14.6% to 30.9%. Therefore, clinicians should be encouraged to check for additional causes of these aberrant free T4 entities. The largest challenge is not to miss serious underlying conditions like secondary hypothyroidism. We present a possible strategy for analyse
hyperthyroxinemia and hypothyroxinemia in combination with a normal TSH. We believe it is important to deploy a similar strategy in guidelines about thyroid disorders. Future studies on this topic should be performed to gain more insight about the best way to follow-up on this condition.

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DISCLOSURES

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

REFERENCES


Van Veggel et al. Occurrence of an aberrant free T₄ with a normal TSH.
Management of *S. aureus* bacteraemia in the Netherlands; infectious diseases consultation improves outcome

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ABSTRACT

Background: *Staphylococcus aureus* bacteraemia is associated with a high mortality rate. Previously it has been shown that consultation by an internist-infectious diseases specialist (IDS) improves the outcome of patients. In this study, we evaluated the differences in management and outcome between patients with, and those without IDS consultation.

Methods: All adult patients with a positive blood culture for *S. aureus* from January 2010 to December 2013 were retrospectively identified with the electronic registration system of our Laboratory for Medical Microbiology. Clinical and microbiological characteristics were retrieved from the electronic patient files, as well as information on bedside consultation by an IDS.

Results: A total of 234 patients with *S. aureus* bacteraemia were included in the study, of whom 77.8% were consulted by an IDS. Management of patients with IDS consultation was more often according to guidelines than was the case without consultation by an IDS; follow up blood cultures were taken more often (97.8% vs. 80.8%, p < 0.001), patients received echocardiography more often (70.9% vs. 50.0%, p = 0.007), and they were more often treated adequately (86.6% vs. 59.2%, p < 0.001). The detection rate of complications in the IDS group was higher (59.3% vs. 32.7%, p = 0.001) and 30-day mortality rate was lower (12.1% vs. 23.1%, p = 0.04). This was confirmed by multivariate analysis.

Conclusion: In patients with a *S. aureus* bacteraemia, bedside consultation by an IDS results in better adherence to diagnostic and treatment guidelines, with higher detection of complications and a higher survival rate.

KEYWORDS

Bacteraemia, infectious diseases consultation, *Staphylococcus aureus*

INTRODUCTION

Bacteraemia caused by *Staphylococcus aureus* is often accompanied by complications and associated with a high mortality rate, even when adequate therapy is given.¹,⁴ The number of cases with *Staphylococcus aureus* bacteraemia (SAB) has increased over the past 25 years.⁵,⁶ Apart from known risk factors such as colonization with *S. aureus*, (treatment of) malignancy, prior hospitalization within 30 days of onset of illness and surgical wounds or trauma, this may be due to the increasing use of haemodialysis, and (intra-vascular) prosthetic devices.⁷,⁸ The frequency of metastatic complications from SAB is high, ranging from 27% to 53%.¹⁰,¹²,¹³ In community acquired SAB, metastatic complications are more common and tend to be more severe. This is probably due to late presentation, late diagnosis and delayed treatment of the bacteraemia.¹⁴,¹⁵ Internationally, a number of recommendations have been formulated regarding the management of SAB.¹⁶,¹⁷ Major priorities are obtaining multiple follow up blood cultures, performing imaging like echocardiography, right choice and sufficient duration of antibiotic treatment, as well as bedside consultation by an infectious diseases specialist of every patient with SAB.¹⁸,¹⁹ Furthermore, recent developments show that an FDG/PET-CT scan can be helpful to detect metastatic infections of SAB, although this technique has not yet been implemented in international SAB management guidelines.²⁰
In our hospital, the department of medical microbiology recommends to all physicians treating patients with SAB to consult an internist-infectiologist, being the consultant infectious diseases specialist (IDS), in order to improve outcome. The aim of this study was to compare the management and outcome of SAB between patients with and without bedside IDS consultation and to determine whether the previously noted international guidelines were followed.

MATERIAL AND METHODS

Study design and setting
We conducted a retrospective study in the Maastricht University Medical Centre+ (MUMC+), a tertiary care university hospital in The Netherlands with a capacity of 715 beds and all facilities, including neurosurgery and cardiothoracic surgery.

Patients
All adult patients (18 years or older) with a positive blood culture for S. aureus in the period of 1 January 2010 to 31 December 2013 were included. Exclusion criteria were poly-microbial blood cultures (with the exception of coagulase negative staphylococci (CNS), which were considered to be contamination), lost to follow-up, no antibiotic treatment of the bacteraemia, and no hospital admission.

Data collection
All blood cultures positive for S. aureus were identified with the laboratory registration system Philips Labosys (Philips Medical Systems, Eindhoven, the Netherlands). Standardized case report forms were used to extract the data from the hospital charts. We recorded baseline characteristics, underlying diseases, comorbidities and prosthetic material.

All microbiologic data, including negative blood cultures, were recorded, as was imaging specifically performed for SAB diagnostics. Suspected primary focus of the bacteraemia and metastatic complications (including endocarditis and vertebral osteomyelitis) were based on the conclusion in the patient charts and/or radiological findings. Next to this, choice of antibiotic therapy and duration of treatment were noted, as well as information whether or not an IDS was consulted. Of all patients, a Fowler score was calculated based on clinical variables that describe the probability of complicated SAB, with a maximum of five points. Two points can be given for a positive follow-up blood culture at 48-96 hours, and one point can be given for each of the following: skin examination findings identifying an acute systemic infection, persistent fever at 72 hours and community acquired (CA) SAB.

Definitions
(CA) SAB was defined as a positive blood culture taken within 48 hours of admission, hospital acquired (HA) SAB as a positive blood culture taken more than 48 hours after admission, and healthcare associated (HCA) SAB as a positive blood culture taken within 48 hours of admission from patients who had been admitted to a hospital or nursing home within the previous three months, patients who were haemodialysis dependent, wore a permanent intravascular catheter, or underwent intermittent chemotherapy. Uncomplicated SAB was defined as a catheter-related bloodstream infection with negative results of follow-up blood cultures at 48 to 96 hours after starting antibiotic treatment, no persistent fever after 72 hours of therapy, and no signs or symptoms of metastatic infection. Complicated SAB was defined as a bacteraemia with a positive follow-up blood culture with S. aureus at 48 to 96 hours, or persistent fever after 72 hours of therapy, or signs or symptoms of metastatic complications.

Metastatic complications were defined as a positive microbiological culture with S. aureus from a previously sterile site, from abscesses or from removed foreign bodies. In addition, radiographic abnormalities suggesting haematogenous spread of the infection were also classed as metastatic complications.

Consultation by an infectious disease specialist was defined as consultation for the purpose of management of SAB during the initial hospitalization. If SAB developed while infectious diseases consultation was already in place for another reason, the date of first positive blood culture was taken as the consultation initiation date. The choice of antibiotic treatment was defined as adequate when the cultured S. aureus isolate was susceptible to the chosen antibiotic therapy.

Our local Dutch guidelines are similar to the international guidelines. Both the Infectious Disease Society of America (IDSA) and the Dutch Working Party on Antibiotic Policy (Dutch acronym: SWAB) recommend a four to six week treatment for complicated SAB, depending on the kind of (metastatic) complication. Uncomplicated SAB can be treated by 14 days of adequate antibiotic therapy, at least seven days intravenously. Furthermore, major priorities are obtaining multiple follow up blood cultures, performing imaging such as echocardiography, and the appropriate choice and sufficient duration of antibiotic treatment. Therapy failure was defined as a positive blood culture with S. aureus for 10 or more days after the start of adequate antibiotic therapy, or relapse of infection, which was defined as a positive blood culture with S. aureus within 12 weeks after the completion of antibiotic therapy.

Statistical analysis
Statistical analysis was performed with IBM SPSS version 21 (SPSS Inc., Chicago, IL, USA) software. Continuous
variables were reported as median with interquartile range (IQR), and categorical variables as proportions. Comparisons between two groups were done using a Mann-Whitney test for continuous data and the Fisher exact test for categorical data. The log-rank test was used to test for differences in survival. Multiple regression analysis for mortality was performed with variables of clinical importance for mortality, such as risk factors for complicated SAB, imaging (TEE and FDG-PET/CT) and IDS consultation. P-values < 0.05 were considered statistically significant.

Ethical approval
This study was reviewed and approved by the Medical Ethical Committee of the Maastricht University Medical Centre+.

RESULTS
During the four year study period, a total of 826 positive blood cultures with \textit{S. aureus} were identified with the laboratory registration system, representing 333 SAB episodes. Of these 333 SAB episodes, 99 episodes were excluded, due to an age < 18 years (n = 43), poly-microbial blood culture (n = 31), no admission (n = 3), no treatment (n = 8), death before blood cultures became positive (n = 11) and lost to follow-up (n = 3). After exclusion, 234 episodes of SAB of 234 patients remained. Of these 234 episodes, 59 (25.2%) were community acquired, 101 (43.2%) hospital acquired, and 74 (31.6%) healthcare associated (figure 1). Table 1 shows the baseline characteristics of the 234 patients included. In total, more males (65%) than females were diagnosed with SAB (152 vs. 82). Consultation by an IDS during the bacteraemia took place in 182 (77.8%) patients. Median time to consultation after drawing blood cultures that first yielded \textit{S. aureus} was three days with an interquartile range of two to five days (table 2). Patients with a community acquired SAB were consulted by an IDS more frequently.

Management
The number of IDS consultations increased in the period from 2010 to 2013; from 58.8% in 2010 to 95.2% in 2013 (figure 2). Management of patients with IDS consultation was more often in accordance with guidelines, compared to patients without consultation. Follow-up blood cultures were obtained more frequently from consulted patients, and they more often underwent diagnostic procedures such as TTE (transthoracic echocardiography), FDG/PET-CT scans, and/or MRI scans. Furthermore, the consulted group was more often treated adequately with respect to both duration and choice of antibiotic treatment (e.g. no addition of gentamicin in prosthetic valve endocarditis was defined as inadequate), compared to those without consultation (156/176 (88.6%) vs. 29/49 (59.2%), p = < 0.001) (table 2).

Figure 1. Flow chart of patient selection

<table>
<thead>
<tr>
<th>Total positive blood cultures, n = 826</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total episodes, n = 333</td>
</tr>
<tr>
<td>Exclusion, n = 99</td>
</tr>
<tr>
<td>- Age &lt; 18 years, n = 43</td>
</tr>
<tr>
<td>- Poly-microbial blood culture, n = 31</td>
</tr>
<tr>
<td>- No admission, n = 3</td>
</tr>
<tr>
<td>- No treatment, n = 8</td>
</tr>
<tr>
<td>- Lost to follow-up, n = 3</td>
</tr>
<tr>
<td>- Died before BC became positive, n = 11</td>
</tr>
<tr>
<td>234 episodes included (234 patients)</td>
</tr>
<tr>
<td>CA n = 59 (25.2%)</td>
</tr>
<tr>
<td>HA n = 101 (43.2%)</td>
</tr>
<tr>
<td>HCA n = 74 (31.6%)</td>
</tr>
</tbody>
</table>

CA = community acquired; HA = hospital acquired; HCA = healthcare associated.
Complications and relapse

The consulted group was more often diagnosed with complicated SAB, (108/182 (59.3%) vs. 17/52 (32.7%), p = 0.001). Likewise, the Fowler score was higher (median 1 day vs. 0 days, p = 0.002), and metastatic complications were more frequently detected (82/182 (45.1%) vs. 10/52 (19.2%), p = 0.001). There was no difference in therapy failure or relapse of infection, although there were only few relapses (table 2).

Seven patients had a relapse of SAB. Table 3 shows the characteristics of these seven patients. During the initial SAB, five of these patients were consulted by an IDS (5/182: 2.7%), all of whom were treated adequately, and echocardiography was performed in all (5/5 TEE; 4/5 TEE).

Mortality

Despite the higher number of detected metastatic complications, the 30-day mortality was lower in the consulted group, compared to the group without consultation (22/182 (12.1%) vs. 12/52 (23.1%), p = 0.04). This was confirmed in the multivariate regression analysis (table 4). In addition, performing an FDG/PET-CT scan was also associated with lower mortality. As expected, higher age and ICU admittance were associated with higher mortality.

**DISCUSSION**

In this evaluation of the management of SAB, we have shown that routine bedside IDS consultation in patients with SAB is associated with better adherence to treatment guidelines and a lower overall mortality rate. Some key diagnostic priorities in the management of SAB, such as follow-up blood cultures and echocardiography in every patient with SAB, were more frequently performed where an IDS was consulted. This resulted in a higher detection rate of disseminated disease, but not in an increased mortality rate. This is possibly due to more adequate management and treatment of patients with IDS consultation.

Subsequently, as patients without IDS consultation were more often treated inadequately, one would also expect more relapses in this group. However, only a low number of relapses (7/234, 3.0%) was detected in this study. Echocardiography is routine diagnostic care in patients with complicated SAB. FDG/PET-CT scans, however, are not (yet) a standard recommendation in the management of patients with complicated SAB.7 Nevertheless, the implementation of an FDG/PET-CT scan as a standard procedure for all patients with complicated SAB and risk factors for dissemination is advocated, as FDG/PET-CT scanning detects more disseminated disease.7,20 Also, performing an FDG/PET-CT scan was associated with lower mortality in our study.

In patients consulted by IDS a higher number of metastatic complications was detected. This is most probably due to the better adherence to guidelines by the consulted IDS. Since follow-up blood cultures were obtained more often and more diagnostic procedures (echocardiography, FDG/PET-CT scans, and MRI scans) were performed, more metastatic complications actually came to light. Another reason could be that patients who were more severely ill were consulted by an IDS more frequently. This bias could not completely be evaded, bedside IDS consultation has

### Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>n (%)</th>
<th>IDS consultation n = 182</th>
<th>No IDS consultation n = 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>115 (63.2)</td>
<td>37 (71.2)</td>
</tr>
<tr>
<td>Age (years), median [IQR]</td>
<td>64 [54-75]</td>
<td>66 [58-76]</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valve pathology</td>
<td>23 (12.6)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>29 (15.9)</td>
<td>19 (36.5)</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>9 (4.9)</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>Post-operative</td>
<td>29 (15.9)</td>
<td>10 (19.2)</td>
</tr>
<tr>
<td>Prosthetic devices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopaedic prosthesis</td>
<td>19 (10.4)</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>Prosthetic heart valve</td>
<td>18 (9.9)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>Intra cardiac device</td>
<td>16 (8.8)</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>Permanent vascular prosthesis</td>
<td>22 (12.1)</td>
<td>3 (5.8)</td>
</tr>
<tr>
<td>Intravascular catheter</td>
<td>38 (20.9)</td>
<td>9 (17.3)</td>
</tr>
<tr>
<td>Onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community acquired SAB</td>
<td>51 (28.0)</td>
<td>8 (15.4)</td>
</tr>
<tr>
<td>Hospital acquired SAB</td>
<td>73 (40.1)</td>
<td>28 (53.8)</td>
</tr>
<tr>
<td>Healthcare associated SAB</td>
<td>58 (31.9)</td>
<td>16 (30.8)</td>
</tr>
<tr>
<td>Focus of infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravascular (non-endocarditis)</td>
<td>42 (23.1)</td>
<td>11 (21.2)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>6 (3.3)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Skin and soft tissue</td>
<td>46 (25.3)</td>
<td>12 (23.1)</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>21 (11.5)</td>
<td>9 (17.3)</td>
</tr>
<tr>
<td>Vertebral osteomyelitis</td>
<td>10 (5.5)</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Other</td>
<td>18 (9.9)</td>
<td>5 (9.6)</td>
</tr>
</tbody>
</table>

SAB = Staphylococcus aureus bacteraemia

Cobussen et al. Management of S. aureus bacteraemia.
Table 2. Univariate analysis of management and outcome

<table>
<thead>
<tr>
<th></th>
<th>IDS consultation n = 182</th>
<th>No IDS consultation n = 52</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to consultation (days)</td>
<td>3 (2-5)</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td><strong>Admission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical ward</td>
<td>121 (66.5)</td>
<td>31 (59.6)</td>
<td>0.41</td>
</tr>
<tr>
<td>Surgical ward</td>
<td>60 (33.0)</td>
<td>21 (40.4)</td>
<td>0.33</td>
</tr>
<tr>
<td>ICU admission</td>
<td>48 (26.4)</td>
<td>17 (32.7)</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Blood culture</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow up blood culture</td>
<td>178 (97.8)</td>
<td>42 (80.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time to first follow up blood culture (days)</td>
<td>2 [1-3]</td>
<td>2 [1-3]</td>
<td>0.23</td>
</tr>
<tr>
<td>Duration of positive blood culture (days)</td>
<td>1 [1-2]</td>
<td>1 [1-1]</td>
<td>0.06</td>
</tr>
<tr>
<td>MRSA</td>
<td>2 (1.1)</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Diagnostics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTE</td>
<td>128 (70.3)</td>
<td>23 (44.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>TEE</td>
<td>33 (18.3)</td>
<td>4 (7.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>FDG/PET-CT scan</td>
<td>27 (14.8)</td>
<td>1 (1.9)</td>
<td>0.008</td>
</tr>
<tr>
<td>MRI-scan</td>
<td>29 (15.9)</td>
<td>1 (1.9)</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inadequate therapy (both duration and choice of antibiotic)*</td>
<td>18/176 (10.2)</td>
<td>20/49 (40.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Duration of therapy (days), total*</td>
<td>20 [15-46]</td>
<td>15 [10-25]</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>• Duration of therapy (days), uncomplicated</td>
<td>16 [14-18]</td>
<td>15 [9-18]</td>
<td>0.16</td>
</tr>
<tr>
<td>• Duration of therapy (days), complicated</td>
<td>44 [19-53]</td>
<td>23 [11-46]</td>
<td>0.02</td>
</tr>
<tr>
<td>Therapy failure</td>
<td>28/176 (15.9)</td>
<td>8/47 (17.0)</td>
<td>0.83</td>
</tr>
<tr>
<td>Relapse</td>
<td>5 (2.7)</td>
<td>2 (3.8)</td>
<td>0.65</td>
</tr>
<tr>
<td><strong>Metastatic complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fowler score</td>
<td>1 [0-2]</td>
<td>0 [0-1]</td>
<td>0.002</td>
</tr>
<tr>
<td>Complicated SAB</td>
<td>108 (59.3)</td>
<td>17 (32.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total metastatic complications</td>
<td>82 (45.1)</td>
<td>10 (19.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>• Endocarditis</td>
<td>15 (8.2)</td>
<td>1 (1.9)</td>
<td>0.21</td>
</tr>
<tr>
<td>• Vertebral osteomyelitis</td>
<td>14 (7.7)</td>
<td>1 (1.9)</td>
<td>0.20</td>
</tr>
<tr>
<td>• Arthritis</td>
<td>8 (4.4)</td>
<td>0</td>
<td>0.21</td>
</tr>
<tr>
<td>• Cerebral</td>
<td>4 (2.2)</td>
<td>1 (1.9)</td>
<td>1.0</td>
</tr>
<tr>
<td>• Deep tissue</td>
<td>13 (7.1)</td>
<td>2 (3.8)</td>
<td>0.53</td>
</tr>
<tr>
<td>• Intravascular (non-endocarditis)</td>
<td>16 (8.8)</td>
<td>3 (5.8)</td>
<td>0.58</td>
</tr>
<tr>
<td>• Osseous (non-vertebral osteomyelitis)</td>
<td>4 (2.2)</td>
<td>1 (1.9)</td>
<td>1.0</td>
</tr>
<tr>
<td>• Multiple</td>
<td>11 (6.0)</td>
<td>1 (1.9)</td>
<td>0.47</td>
</tr>
<tr>
<td>• Other ‡</td>
<td>6 (3.3)</td>
<td>0</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-day mortality</td>
<td>22 (12.1)</td>
<td>12 (23.1)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

IDS = infectious diseases specialist; MRSA = methicillin resistant *Staphylococcus aureus*; TTE = transthoracic echocardiography; TEE = transoesophageal echocardiography; SAB = *Staphylococcus aureus* bacteraemia

* In n = 9 patients the duration of antibiotic therapy was missing (n = 5 in the group with IDS consultation and n = 4 in the group without consultation
† Osseous metastatic complications: infected osteosynthesis implant (n = 4), non-vertebral osteomyelitis (n = 1)
‡ Other metastatic complications: respiratory (n = 2), staphylococcal scalded skin syndrome (SSSS) (n = 3), infected bone marrow (n = 1), prostatitis with abscess (n = 1), nephritis (n = 1)
Figure 2. Number of consultations per year

Table 3. Characteristics of 7 patients with relapse of SAB

<table>
<thead>
<tr>
<th>No.</th>
<th>Bacteraemia, initial focus</th>
<th>Comorbidities</th>
<th>IDS-c</th>
<th>FU-BC/duration positive BC (days)</th>
<th>FDG/PET-CT scan</th>
<th>Fowler score</th>
<th>Antibiotic therapy, iv/oral (days)</th>
<th>Adequate therapy</th>
<th>Time to relapse (days)</th>
<th>Complications during relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HA SAB, unknown focus</td>
<td>DM type II</td>
<td>Yes</td>
<td>Yes / 3</td>
<td></td>
<td>No</td>
<td>4</td>
<td>Amoxi/clav, 3/0 + Flucloxacillin, 17/0 + Clindamycin, 0/11</td>
<td>Yes</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>HA SAB, intravascular line focus</td>
<td>Malignancy</td>
<td>Yes</td>
<td>Yes / 1</td>
<td></td>
<td>No</td>
<td>2</td>
<td>Amoxi/clav, 2/0 + Flucloxacillin 16/0 + Gentamicin, 5/0</td>
<td>Yes</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>CA SAB, skin and soft tissue focus</td>
<td>DM type II, ICM</td>
<td>Yes</td>
<td>Yes / 3</td>
<td></td>
<td>No</td>
<td>4</td>
<td>Amoxi/clav, 2/0 + Flucloxacillin, 15/0 + Clindamycin, 2/14</td>
<td>Yes</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>CA SAB, unknown focus</td>
<td>DM type II</td>
<td>No</td>
<td>Yes / 5</td>
<td></td>
<td>No</td>
<td>4</td>
<td>Amoxi/clav, 2/0 + Flucloxacillin, 9/0 + Gentamicin, 6/0</td>
<td>No</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>HA SAB, mediastinitis focus</td>
<td>ICM, malignancy, post-CABG</td>
<td>No</td>
<td>Yes / 1</td>
<td></td>
<td>No</td>
<td>0</td>
<td>Amoxi/clav, 1/0 + Pip/tazo, 7/0</td>
<td>No</td>
<td>11</td>
</tr>
<tr>
<td>6</td>
<td>HCA SAB, skin and soft tissue focus</td>
<td>DM type II, HD</td>
<td>Yes</td>
<td>Yes / 1</td>
<td></td>
<td>No</td>
<td>1</td>
<td>Flucloxacillin, 17/0 + Gentamicin, 2/0</td>
<td>Yes</td>
<td>74</td>
</tr>
<tr>
<td>7</td>
<td>HA SAB, intravascular line focus</td>
<td>DM type II, ICM</td>
<td>Yes</td>
<td>Yes / 6</td>
<td></td>
<td>Yes</td>
<td>3</td>
<td>Flucloxacillin, 18/0</td>
<td>Yes</td>
<td>18</td>
</tr>
</tbody>
</table>

FU-BC = follow-up blood culture; BC = blood culture; IDS-c = consultation by an infectious diseases specialist; iv = intravenous; CA = community acquired; HA = hospital acquired; HCA = healthcare associated; SAB, Staphylococcus aureus bacteraemia; DM = diabetes mellitus; ICM = ischemic cardiomyopathy; Amoxi/clav = amoxicillin/clavulanic acid; Pip/tazo = piperacillin/tazobactam; PM = pacemaker
been implemented routinely in all patients with SAB in our hospital, particularly in recent years (95.2% of patients with SAB in 2013). The number of patients who were consulted by an IDS rose during the years studied, from 58.8% in 2009 to 95.2% in 2013. This is probably due to the expansion of the infectious disease specialist team at the end of 2011. Furthermore, stricter rules were agreed upon between the internist-infectiologists (IDS) and the medical microbiologist concerning infectious diseases consultations. These included making the internist-infectiologist aware of all blood cultures positive for 
*Staphylococcus aureus*, so these patients received IDS consultation whether the treating physician asked for it or not. Also, ICU patients and patients in the hematology ward, who were previously consulted by the medical microbiologist by telephone, from then on received a bedside consultation by the IDS.

Median time to bedside consultation, after the blood cultures which were to yield *S. aureus* were drawn, was three days. This delay was caused by the fact that the bacteria in the culture need to grow to be noticed, which is often after one to two days. However, a contributing factor to an even longer delay in some patients could be that no bedside consultations were done in the weekends. In the last years of the study, with expansion of the IDS team and strict bedside consultations in almost all patients, time to consultation decreased compared to the early years of the study (2010-2011: median 4 days, mean 5 days, 2012-2013: median 3 days, mean 3 days).

The treating physician bore the main responsibility for the management of the patient with SAB and all IDS advices were on a consular basis. Because the treating physician and the IDS occasionally disagreed, the recommendations of the IDS were not always executed. Therefore, despite an IDS consultation, management of patients consulted by an IDS was not always optimal, including inadequate duration of treatment and no echocardiography in all patients. Despite the higher number of metastatic complications in the group with IDS consultation, the 30-day mortality was lower (12.1% vs. 23.1%, *p = 0.04*), as was confirmed in our multivariate analysis and previously has been shown in other studies.\textsuperscript{11,14,14-16}

There are some limitations to our study. First, this being a single centre retrospective study, we nonetheless included almost 250 patients in the four year study period. Furthermore, no distinction was made between the separate components of the IDS consult such as recognition of endocarditis stigmata, correctly obtaining follow-up blood cultures and diagnostics, and appropriate and adequate administration of antibiotics. Next to this, we had to rely on the completeness of the charts. During the last three years of the study period, the hospital used electronic patient files, which improved the availability of data. In addition, the investigators were not blinded to IDS consultation. Therefore, we used strict definitions to minimize any potential bias. Another limitation might be that patients who were discharged in a clinically good condition, may have developed metastatic complications or a relapse at home without referral to our clinic. Since our hospital serves both as a secondary and tertiary referral centre, follow-up after discharge will most likely be done in our hospital, but we can’t rule out that a SAB complication was treated in another hospital and was therefore missed in our analysis.

In conclusion, our study shows the need for bedside IDS consultation in every patient with SAB. Consultation by an IDS results in better adherence to management guidelines and detection of more metastatic complications with better overall survival. Therefore, in patients with SAB, bedside consultation by an IDS should be obligatory.

**Acknowledgments**

We want to thank the ICU and the Medical Archives for their contributions to the data collection, and John Penders of the department of Medical Microbiology for his help with the statistical analysis.

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**Table 4. Multivariate regression analysis of mortality**

<table>
<thead>
<tr>
<th>Variables</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.11 (1.06-1.16)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.91 (0.34-2.54)</td>
<td>0.88</td>
</tr>
<tr>
<td>CA vs. HA SAB</td>
<td>1.07 (0.28-4.06)</td>
<td>0.92</td>
</tr>
<tr>
<td>CA vs. HCA SAB</td>
<td>2.56 (0.57-11.61)</td>
<td>0.22</td>
</tr>
<tr>
<td>Duration of positive BC</td>
<td>0.82 (0.61-1.08)</td>
<td>0.16</td>
</tr>
<tr>
<td>Fowler score</td>
<td>1.84 (1.13-2.97)</td>
<td>0.014</td>
</tr>
<tr>
<td>Medical Ward</td>
<td>0.13 (0.03-0.47)</td>
<td>0.002</td>
</tr>
<tr>
<td>ICU admission</td>
<td>10.43 (3.38-32.13)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IDS consultation</td>
<td>0.36 (0.13-0.98)</td>
<td>0.046</td>
</tr>
<tr>
<td>TEE</td>
<td>0.32 (0.07-1.50)</td>
<td>0.15</td>
</tr>
<tr>
<td>FDG/PET-CT scan</td>
<td>0.07 (0.01-0.84)</td>
<td>0.036</td>
</tr>
<tr>
<td>Metastatic complications</td>
<td>0.45 (0.12-1.72)</td>
<td>0.24</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>2.06 (0.26-16.36)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

CA = community acquired; HA = hospital acquired; SAB = *Staphylococcus aureus* bacteraemia; HCA = health care associated; BC = blood culture; ICU = intensive care unit; IDS = infectious diseases specialist; TEE = transoesophageal echocardiography.
D I S C L O S U R E S

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R E F E R E N C E S

Coronary artery spasms due to tyrosine kinase inhibitors used in chronic myeloid leukemia


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ABSTRACT

Tyrosine kinase inhibitors (TKIs) have changed the landscape of treatment for patients with chronic myeloid leukemia (CML) leading to a life expectancy comparable to the general population. Side effects commonly encountered during TKI treatment are pleural effusion due to use of dasatinib and vascular side effects due to nilotinib and ponatinib. Coronary artery spasm (CAS), although encountered during treatment with other chemotherapeutic drugs, have to our knowledge never been reported during TKI treatment. Here, we describe two cases of coronary artery spasms which are likely due to TKIs.

KEYWORDS
Tyrosine kinase inhibitors, chronic myeloid leukemia, BCR-ABL, coronary artery spasms, off-side inhibitions

CASE SERIES

Patient A
A 54-year-old Caucasian male with CML in chronic phase (CP) was admitted to the ICU of our hospital after a successful resuscitation because of an out-of-hospital cardiac arrest in June 2013. His CML was first diagnosed in January 2005 and treated with imatinib 400 mg o.d. after brief use of hydroxyurea. Due to lack of cytogenetic response, his treatment was switched to dasatinib 50 mg b.d. resulting in a major molecular response (MR3, BCR-ABL ≤ 0.1%). Unfortunately, in July 2010 he developed pleural effusion treated with furosemide, thoracentesis and dose reduction of dasatinib (40 mg b.d.). In January 2013, the pleural effusion relapsed and nilotinib 300 mg b.d. was started in February 2013 while still on a MR 3.

In June 2013, he complained of transient chest pain at the out-patient clinic. A cardiac consultation was planned for the next day and acetylsalicylic acid and metoprolol were directly initiated. However, the following night he collapsed with ventricular fibrillation as first recorded rhythm. After defibrillation, ECGs showed transient signs of anterior wall infarction (figure 1) and normal QTc. A coronary angiography (CAG) was subsequently performed, which showed clear signs of coronary artery spasms (CAS) responsive to intracoronary nitroglycerine and no coronary narrowing related to arteriosclerosis (figure 2). Post-resuscitation cardiac troponin-T showed a typical rise and fall with a maximum of 863 ng/l (normal value: < 14 ng/l). Later that day a new ECG showed ST-elevation corroborative with inferoposterolateral infarction but again normalized after vasodilatory treatment. No other explanation for CAS (hypomagnesemia or known offending agents) was present. So, in a short period of time two different areas of the heart were briefly exposed to severe ischemia in the absence of stenotic coronary artery disease. During the ICU admission nilotinib was temporarily halted. As a measure of secondary prevention of sudden cardiac death, a cardioverter-defibrillator (ICD) was implanted before discharge. In July 2013 two days after nilotinib restart, the patient was re-admitted to the cardiac care unit with acute chest pain. The ECG showed transient inferior ST-segment elevation indicative of CAS. A causal relation with nilotinib use was now strongly suspected (Common
Terminology Criteria for Adverse Events (CTCAE grade 4),
supporting the switch to bosutinib 500 mg o.d., which is
considered to have fewer cardiac side-effects.

Two years later he experienced a similar episode of
acute chest pain, without irregularities on CAG,
probably due to CAS this time caused by bosutinib.
After optimizing isosorbide mononitrate dosing and
bosutinib dose reduction to 300 mg o.d. with persistence
of MR4.5 (BCR-ABL ≤ 0.01%) the patient remained free of
complaints.

Patient B
Patient B is a 46-year-old Caucasian male, first diagnosed
with CML in blast crisis (BC) in January 2013 for which
nilotinib 400 mg b.d. was given. In April 2013, he received
an allogeneic T-cell depleted stem cell transplantation
with a matched unrelated donor after myeloablative
conditioning followed by a pre-emptive donor lymphocyte
infusion (DLI).

In December 2013 he presented with headache, caused
by a central nervous system (CNS) CML blast relapse
without signs of a systemic relapse. He was treated with
liposomal cytarabine intrathecally combined with oral
dexamethasone and dasatinib 140 mg o.d. resulting
in a complete remission. A second CNS relapse in
February 2014 was treated with dasatinib dose increase to
180 mg o.d. and liposomal cytarabine was readministered
intrathecally, followed by craniospinal radiation therapy (33
Gy) and therapeutic DLI. After radiation therapy, dasatinib
was restarted at a dose of 100 mg o.d. without further
evidence of CNS relapse ever since.

Figure 1. ECG of patient A with ventricular fibrillation (above) and ischemia (below)

Figure 2. Coronary arteriogram of patient A: left showing coronary artery spasm and right showing resolving of the spasm after intracoronary nitroglycerine
Before transplantation ECG analysis indicated signs of a previous inferior wall infarction with pathological Q-waves. Although confirmed by echocardiography, no secondary prophylaxis was started.

In February 2016, he presented with acute chest pain typical for angina pectoris without ECG changes at the cardiac emergency department. Repeatedly, cardiac biomarkers were normal and the patient was discharged for further outpatient analysis. According to guidelines, carbasalate calcium, metoprolol and simvastatin were started. As the patient refused coronary angiogram, conservative therapy was intensified by adding nifedipine. Adenosine stress cardiac MR imaging revealed ischemia in mid-anterolateral and mid-inferior segments without new electrocardiographic changes.

A few weeks later he was again admitted to the coronary care unit with acute chest pain. Now his ECG showed ST-segment depression in V2-V5 with ST-segment resolution after intravenous nitroglycerin (figure 3). His QTc was 431 ms. Cardiac troponin-T showed a typical rise and fall with a maximum of 768 ng/l. It was concluded that the patient suffered a non-STEMI. For risk stratification a CAG was performed. The right coronary artery (RCA) showed an evident ostial lesion, which significantly regressed after intracoronary nitroglycerine. In the left mid-anterior descending

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**Figure 3.** ECG of patient B showing ST-segment depression in V2-V5 (above) with ST-segment resolution after intravenous nitroglycerin (below)
artery (LAD) a long trajectory of stenosis (maximum stenosis of 60%) was observed, fractional flow reserve (FFR) assessment of this trajectory showed a significant pressure drop after intravenous adenosine, indicative of ischemia. The circumflex artery was occluded and was considered a chronic occlusion given the rather extensive collateral network from the RCA and LAD. A FFR-guided percutaneous coronary intervention (PCI) of the intermediate lesion mid LAD was performed because of suspected ischemia in the anterolateral wall, also in accordance with the previous stress MR imaging findings. Strikingly, the fractional flow reserve measurement after PCI was actually worse than before, which raised suspicion of a different etiology than a flow-limiting atherosclerotic lesion, i.e. CAS. A switch to conservative medical treatment was decided upon.

Nevertheless, after the PCI the patient experienced recurrent episodes of anginal pain, Canadian Cardiovascular Society class IV, with ST-depression in V2-V5 on ECG. On every occasion he responded quickly to nitroglycerin, without angina pectoris on exertion afterwards. A CAG was repeated showing that the stent in the LAD was patent with normal flow. In the proximal RCA significant spasm occurred again that disappeared after nitroglycerine administration. Despite treatment with verapamil and isosorbide mononitrate his acute chest symptoms kept recurring. It was hypothesized that recurrent vasospasms of the RCA compromised the collateral flow to the circumflex artery causing ischemia. In the absence of hypomagnesemia and satisfactory effects of vasodilatory drugs, an attempt to open the circumflex artery failed. Following the observations in patient A, dasatinib was considered a potential offending agent (CTCAE grade 3). In absence of other treatment options of TKI that cross the blood-brain barrier, and in an attempt to reduce symptoms, dasatinib dosage was lowered to 70 mg o.d. With a dasatinib level of 3.38 ug/l (target range 1.4-3.4 ug/l) BCR-ABL1 MR 4.5 persisted.

In September 2016, the patient developed pleural effusion, for which dasatinib was temporarily ceased and prednisolon was started with excellent result. In that period he remained free of anginal complaints, in support of the role of dasatinib with respect to his complaints. Restarting dasatinib immediately induced new episodes of angina pectoris. Anti-vasospasm therapy was intensified by adding nicorandil keeping a MR 4.5 while on dasatinib.

DISCUSSION

In recent years, TKIs have shifted treatment options for patients with CML, with improved prognosis of patients and life expectancy approaching that of the general population. However, TKI use causes a range of off-target side effects, some of which are well established, i.e. pleural effusion as encountered in both our patients. These side effects are caused by off-target effects on other tyrosine kinases. Cardiac side effects and arterial vascular events including angina pectoris, pericardial effusion, bradycardia, heart failure and QTc prolongation are common due to TKI treatment for CML. Nilotinib and especially ponatinib (around 10%) are more frequently associated with cardiac side effects and arterial vascular events than imatinib, dasatinib and bosutinib (2-5%). The incidence of cardiovascular side effects with TKIs for other indications varies, with higher incidence for VEGF inhibitors, as would be expected, with hypertension in up to 50% of patients and chest pain in 15% of the patients. Other TKIs, like ALK (e.g. crizotinib), JAK2 (e.g. ruxolitinib) and BTK (ibrutinib) inhibitors have low incidence for vascular side effects.

The pathogenesis of arterial vascular events due to TKI treatment appears to be multifactorial, influenced by known pro-atherogenic risk factors like hyperglycemia and hypercholesterolemia, which are even increased by some TKIs (nilotinib). Our patients did not develop hyperglycemia or hypercholesterolemia through TKI treatment. TKIs can change proliferation of endothelial cells and angiogenesis by blocking PDGFR and KIT receptor. Discoidin domain receptor 1 (DDR1) is inhibited by TKIs for CML and plays an important role in plaque formation in arteriosclerosis. Coronary artery spasms have, to our knowledge, never been reported as a side-effect of TKIs in the literature, or to the Dutch medicine evaluation board (Lareb), in contrast to chemotherapeutic drugs such as paclitaxel, capetabine and gemcitabine.
Coronary artery spasms, also known as vasospastic angina or Prinzmetal angina, are caused by focal or diffuse spasm of a coronary artery. This might result in significant temporary obstruction and even myocardial infarction, although short episodes can go unnoticed. The pathogenesis is not entirely understood. Yet, catecholamine activity, chronic inflammation, endothelial dysfunction, availability of nitric oxide, smooth muscle hypercontractibility and activation of the Rho/ROCK pathway seem to play a role. Coronary artery spasms can be accompanied by arrhythmias, including ventricular fibrillation, which seldom subsides spontaneously. Known risk factors for spasms are age, smoking (patient B), hypomagnesaemia, alcohol consumption and stress. For patient A, none of these risk factors were present.

Sorafenib, a TKI to treat renal cell carcinoma and hepatocellular carcinoma is associated with coronary artery spasms. It exerts its cytotoxic effect by inhibition of Raf, but it also inhibits its downstream effectors MEK and ERK regulating cellular proliferation and survival. Coronary artery spasms induced by sorafenib are possibly due to downstream inhibition of MEK which could cause decreased suppression – and, by consequence, the up-regulation – of the Rho/ROCK pathway. Activation of the Rho/ROCK pathway is shown to have an important role in the pathogenesis of coronary artery spasms due to augmentation of Ca\(^{2+}\) release. The Rho/ROCK is also important for cell-cell adhesion. Inhibition of normal c-Abl kinases by STI571 (imatinib mesylate) has been shown to activate the Rho/ROCK pathway and influence cell-cell adhesion. Inhibition of normal c-Abl has been suggested as a contributing cause of cardiotoxicity by imatinib. Inhibition of BCR-ABL1 and normal Abl-kinases with TKIs could possibly lead to up-regulation of the Rho/ROCK pathway, which could play a causative role. No specific treatment is available and hence to the same break in suppression leading to up-regulation of the Rho/ROCK pathway (figure 4). There are to our knowledge no reports about CAS and other inhibitors of the Raf/MEK/ERK pathway, like trametinib, vemurafenib and dabrafenib.

First line treatment for coronary artery spasms consists of high dose long-acting calcium channel blockers such as nifedipine 60 mg/day or diltiazem 360 mg/day. In severe cases non-dihydropyridine calcium-antagonists can be combined with dihydropyridine calcium-antagonists. Other options include fluvastatin treatment, long acting nitrates or nicorandil. The Rho-kinase inhibitor fasudil has also shown to be beneficial in vasospastic angina. Other cardio-vascular risk factors for coronary artery spasms, such as smoking, hypomagnesaemia and use of beta blockers should be avoided if possible. In cases of ventricular fibrillation an ICD implantation should be considered and ischemic heart disease should be treated properly.

In our patients, CAS occurred with the use of nilotinib, dasatinib and bosutinib suggesting a class effect of TKIs used for CML. Since the pathogenesis of coronary artery spasms due to TKIs has not been fully elucidated, it is difficult to choose the best TKI when CAS is encountered. Before starting a TKI the prescribing physician should be aware of the possible vascular side effects and the patient’s cardiovascular risk profile. The European CVD risk assessment score has been shown to predict cardiovascular complications in patients during nilotinib treatment and could be used to assess patients at higher risk for vascular complications. In patients with higher risks, imatinib in first line or bosutinib for second line should be the TKI of choice, due to low off-target inhibition of other tyrosine kinases and lower rate of vascular side effects. In patients with a higher risk or a cardiovascular history we advise monitoring and treatment of cholesterol, glucose, magnesium and blood pressure on a regular basis, combined with obtaining a thorough medical history focused on cardiovascular complaints. In case of CAS and no suitable alternative for TKI, as in patient A, dose reduction could be considered, since other off-target effects like pleural effusion seem to be dose-dependent. Due to the low incidence and unpredictability of CAS, we do not advise prophylactic treatment with calcium channel blockers, even in patients with previous cardiovascular history. Both patients had a moderate risk according to this risk assessment, which in retrospection raises doubts as to whether nilotinib was the best first line treatment in patient A.

**CONCLUSION**

In conclusion, we describe two CML cases with coronary artery spasms related to nilotinib, dasatinib and bosutinib. When patients on TKI present themselves with chest pain, CAS should be considered. Inhibition of BCR-ABL1 and normal Abl-kinases with TKIs could possibly lead to up-regulation of the Rho/ROCK pathway which could play a causative role. No specific treatment is available and standard treatment of coronary artery spasm, including high dose long-acting calcium channel blockers, should be considered. If clinically possible, a switch of TKI or lowering the dose is advocated (Expert opinion). Imatinib seems to be the TKI of choice since this drug possesses the lowest risk of arterial events, showing similar overall survival and response as other TKI (Grade A evidence).

**ACKNOWLEDGEMENTS**

We thank Peter Donnelly for critically evaluating our manuscript for English language.
REFERENCES


Ticking off diagnoses of abdominal pain: early neuroborreliosis with radiculopathy

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ABSTRACT

Lyme disease (LD) is the most common tick-borne illness. The diagnosis of LD is difficult because of the great variation in clinical manifestations. Although abdominal pain is generally not considered a sign of LD, in this case report we describe a patient with unexplained severe abdominal pain that eventually turned out to be LD due to radiculopathy. Since the incidence of LD is rising it is important to realise that severe abdominal pain could be the first clinical manifestation of early neuroborreliosis.

KEYWORDS

Abdominal pain, gastro-intestinal, lyme disease, neuroborreliosis, radiculopathy

INTRODUCTION

Lyme disease (LD), caused by the spirochete Borrelia burgdorferi, is the most common tick-borne illness, with more than 22,000 cases in the Netherlands each year. The clinical presentation of LD varies and about 4% of confirmed cases present with radiculopathy. This usually presents with a painful radicular syndrome but in the case of an isolated thoracic radiculoneuropathy, it may present with abdominal pain and is easily misdiagnosed. Neuroborreliosis is a potentially fatal disease and prompt diagnosis and treatment are important. This case report describes a patient with unexplained abdominal pain that eventually turned out to be LD.

CASE REPORT

A 71-year-old woman was referred to an Emergency Department in the Netherlands for consultation of the gastroenterologist because of severe abdominal pain. Her medical history was unremarkable. Eight weeks before she had suffered from temporary lower back pain, myalgia, fever and varying burning sensations and tenderness on the head and in both upper legs; subsequently she had developed moderate abdominal pain with abdominal distension and diarrhea that was considered a self-limiting gastroenteritis. However, several weeks later progressive abdominal pain occurred with nausea and myalgia. The pain was continuous and sharp, located in the lower abdomen and unrelated to oral intake, defecation or body position. Her vital signs were normal. She was alert and cooperative. There were normal abdominal sounds and there were no signs of peritonitis. Physical examination of the chest, vertebral spine and a general neurologic exam were normal; she had a normal gait, the Laseque’s test was negative and there were no signs of sensory loss. General laboratory tests, except for C-reactive protein 34 mg/l (reference: < 8 mg/l) and leucocytes 11 x 10⁹/l (reference: 4-10 x 10⁹/l), were normal. Urinalysis, blood- and fecal cultures were also normal. Because the abdominal pain...
appeared to be severe without specific signs pointing to a clear diagnosis, a computed tomography (CT) scan of the chest and abdomen was performed to rule out common causes of abdominal pain such as peritonitis, appendicitis, cholecystitis, pancreatitis, intra-abdominal malignancy, ischemic bowel disease, vasculitis and pleural abnormalities. The CT was normal. She was admitted for pain management and further diagnostic workup. A malignancy of the digestive tract and inflammatory and ischemic bowel disease were ruled out by colonoscopy and gastroscopy. MRI of the small intestine was normal. Meanwhile, she developed fever. A whole-body positron emission tomography-CT (PET-CT) scan was performed that revealed no abnormalities. In combination, the ‘normal’ results of the extensive diagnostic tests ruled out the majority of the abovementioned causes.

Going over her history again, she emphasized that she had stayed in a high-endemic area for ticks and had suffered a possible tick bite without any sign of erythema migrans. We decided to test for LD. Serologic tests were consistent with a recent *B. burgdorferi* infection (table 1). Additionally, testing of cerebrospinal fluid confirmed the diagnosis of neuroborreliosis (table 1). As abdominal pain was the only symptom that persisted over a course of several weeks, we concluded this must have been due to radiculoneuropathy. She was treated with ceftriaxone 2 gram intravenously for 2 weeks. After several days the abdominal pain gradually disappeared and she finally fully recovered (table 1).

**DISCUSSION**

Diagnosing LD can be difficult because of the great variation in clinical manifestations. Abdominal pain is generally not considered a sign of LD. Yet, it is important to realize that severe abdominal pain could be the first clinical manifestation of early neuroborreliosis. Neuroborreliosis is a potentially fatal disease and prompt diagnosis and treatment are important. Furthermore, this case demonstrates the necessity of re-examining the medical history of a patient with unexplained clinical signs.

Only a few cases have been described where abdominal pain was a first clinical manifestation of early neuroborreliosis. In these cases, abdominal pain was accompanied by facial paralysis, the so-called Bannwarth syndrome.

Going over her history again, she emphasized that she had stayed in a high-endemic area for ticks and had suffered a possible tick bite without any sign of erythema migrans. We decided to test for LD. Serologic tests were consistent with a recent *B. burgdorferi* infection (table 1). Additionally, testing of cerebrospinal fluid confirmed the diagnosis of neuroborreliosis (table 1). As abdominal pain was the only symptom that persisted over a course of several weeks, we concluded this must have been due to radiculoneuropathy. She was treated with ceftriaxone 2 gram intravenously for 2 weeks. After several days the abdominal pain gradually disappeared and she finally fully recovered (table 1).

**Table 1. Microbiological data**

<table>
<thead>
<tr>
<th></th>
<th>After 8 weeks of abdominal pain</th>
<th>6 Weeks post-treatment</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM antibody <em>Borrelia burgdorferi</em> (AU/ml)</td>
<td>240</td>
<td>0.4</td>
<td>&lt; 1.1 negative</td>
</tr>
<tr>
<td>IgG antibody <em>Borrelia burgdorferi</em> (AU/ml)</td>
<td>0.09</td>
<td>15.1</td>
<td>&lt; 15 negative</td>
</tr>
<tr>
<td>IgG/IgM anti-C6 peptide (index)</td>
<td>8.5</td>
<td>4.3</td>
<td>&lt; 1.1 negative</td>
</tr>
<tr>
<td>IgG antibody <em>Borrelia burgdorferi</em> immunoblot</td>
<td>Moderate positive (VlsE+)</td>
<td>Moderate positive (VlsE+)</td>
<td>Negative</td>
</tr>
<tr>
<td>IgM antibody <em>Borrelia burgdorferi</em> immunoblot</td>
<td>Positive (VlsE+/OspC+)</td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Cerebrospinal fluid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucocytes</td>
<td>1228/mm³ (84% lymphocytes / 11% monocytes)</td>
<td></td>
<td>&lt; 5/mm³</td>
</tr>
<tr>
<td>Protein</td>
<td>2.77 g/l</td>
<td>0.26-0.79 g/l</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>2.15 mmol/l</td>
<td>2.5-3.7 mmol/l</td>
<td></td>
</tr>
<tr>
<td>IgM antibody index <em>Borrelia burgdorferi</em></td>
<td>2.3</td>
<td>&lt; 0.3 negative</td>
<td></td>
</tr>
<tr>
<td>IgG antibody <em>Borrelia burgdorferi</em></td>
<td>19.0</td>
<td>&lt; 3 negative</td>
<td></td>
</tr>
</tbody>
</table>

1DiaSorin LIAISON Borrelia burgdorferi IgG(VISE)/IgM(VISE/OspC); 2Immunogenetics; 3Virotech Europeline; 4IDEIA Oxoid
of radiculitis and pleocytosis of cerebrospinal fluid with specific antibodies against *B. burgdorferi*. Characteristics of early neuroborreliosis are a high production of intrathecal IgM antibody *B. Burgdorferi* and lymphocytic pleocytosis. Although the diagnosis of neuroradiculopathy was not confirmed by electromyography, the quick response to antibiotic therapy further supported it.

Notwithstanding the low sensitivity of serologic tests for detecting early LD, it might be useful to distinguish between early and late LD. In this case the diagnostic tests of blood and CSF indicate an early manifestation of LD, early neuroborreliosis.

Because of unexplained severe abdominal pain, several diagnoses were considered and extensive diagnostic tests were performed. As the combination of normal laboratory tests, abdominal ultrasonography and CT imaging ruled out the majority of these diagnoses as cause of abdominal pain, we consider the endoscopies, MRI of the small intestine and PET-CT to be overdiagnostics. It would have been better to focus on ruling in a diagnosis of LD, because the patient’s symptoms became apparent after a suspected tick bite during a stay in a high-endemic area.

In conclusion, as the incidence of LD rises it is important to realise that severe abdominal pain could be the first clinical manifestation of early neuroborreliosis with radiculopathy. Other clinical clues for this diagnosis are abdominal distension due to abdominal wall weakness, abdominal pain and facial paralysis or cranial neuropathy (Bannwarth syndrome), radiculopathy in one or multiple dermatomes (i.e. pain and dysesthesia) and signs of meningism. Furthermore, instead of doing extensive diagnostic tests, it is important to scrutinize the patient’s medical history in the presence of unexplained clinical signs.

REFERENCES

CASE REPORT

Subacute renal injury in hypothyroidism: a case report of an unusual phenomenon

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ABSTRACT

Severe hypothyroidism is known to cause elevation of creatinine and this phenomenon has been reported in clinical settings in the past. Screening for hypothyroidism is not regularly performed in the differential workup for acute kidney injury due to its rare presentation. Therefore, to most physicians hypothyroidism is not known as a cause of acute kidney injury.

In this clinical case report, we describe a case of subacute kidney injury in a patient with severe hypothyroidism prior to iodine-131 ablation therapy. Hypothyroidism was not recognized as the cause of elevated creatinine, which in this case led to unnecessary hospital admission and diagnostics. This case report serves as a reminder for clinicians to consider hypothyroidism in the differential diagnosis of (sub)acute kidney injury.

KEYWORDS

Hypothyroidism, renal injury, iodine ablation therapy, thyroid hormone withdrawal

INTRODUCTION

Thyroid hormones have a direct effect on almost all body organs. The interplay between thyroid hormone and the kidney is complex. Thyroid hormone directly affects the normal growth and development of the kidney and the kidney in turn has effects on thyroid hormone metabolism and elimination.¹,²

Thyroid hormone is also known to cause changes in hemodynamics, which in the kidney is mediated by changes in the renin-angiotensin-aldosterone system (RAAS) and alterations of the excretion of electrolytes and water.³ In overt hypothyroidism these effects, along with decreased cardiac output and increased vascular resistance, can cause decreased renal blood flow with a subsequent decrease in glomerular filtration rate (GFR).⁴,⁵ In some cases of severe hypothyroidism, reversible acute kidney injury is reported. However, the exact incidence of acute kidney injury in hypothyroidism remains unknown.

Although elevated creatinine due to hypothyroidism has been described in a number of observational studies and case reports, screening for hypothyroidism is not included in the routine workup of acute kidney injury and thus physicians are generally unfamiliar with this phenomenon. As a reminder for clinicians to consider hypothyroidism in the differential diagnosis of acute kidney injury, we offer a case of subacute kidney injury due to hypothyroidism which led to unnecessary hospital admission and diagnostics.

CASE REPORT

A 59-year-old man was referred to our clinic with a nodular mass of the thyroid. His medical history consisted of depression and gastroesophageal reflux disease for which duloxetine and omeprazole had been prescribed. Anamnesis yielded no relevant findings,
besides hoarseness during the last two weeks. The nodular mass of the thyroid was classified as TIRADS-4a, corresponding to a 5-10% chance of malignancy. After biopsy and hemithyroidectomy, the patient was diagnosed with multifocal papillary thyroid carcinoma (TNM stage: T1bN0M0). Patient was scheduled for completion thyroideectomy and radioiodine-131 (I-131) ablation therapy eight weeks after surgery. In accordance to the Dutch guideline levothyroxin therapy was withheld prior to the ablation therapy, resulting in severe hypothyroidism with a thyrotropin above 50 mU/l (assay specific upper limit of detection: 50 mU/l, reference range: 0.3-5.6 mU/l) and an undetectable level of thyroxin. Due to logistic errors, the total time of thyroid hormone withdrawal was eight weeks, which is four weeks longer than recommended by the Dutch guideline.

During thyroid hormone withdrawal, the creatinine level rose to a maximum of 152 μmol/l (reference range: 60-110 μmol/l). Prior to completion thyroideectomy, the creatinine level had been stable at 78 μmol/l. The combination of increased serum creatinine and general discomfort with fatigue and muscle aches being the main complaints, the nephrologist was consulted, who decided to admit the patient to the hospital for further examination. At this time, the patient had been on thyroid hormone withdrawal for seven weeks. Upon admission, there were no signs of inadequate fluid intake or fluid loss. Physical examination showed no change in body weight nor peripheral oedema. At the time of admission there were no signs of hypotension (blood pressure on average 155/85 mmHg) or oliguria. Urine analysis revealed no erythrocyturia, leukocyturia or proteinuria. Post renal obstruction was ruled out by ultrasonography. Omeprazole was the only nephrotoxic medicine prescribed at the time. However, tubulointerstitial nephritis was deemed unlikely due to the chronic use of this drug and absence of other clinical signs such as eosinophilia, leukocyturia or proteinuria. Furthermore, after discontinuation of omeprazole, a further increase of creatinine was observed. The patient was discharged after two days without any changes in creatinine clearance, as at that point hypothyroidism induced kidney injury was suspected. One week later I-131 ablation was performed and hormone replacement therapy (HRT) with levothyroxine was initiated. Four days after HRT was initiated, his creatinine value had decreased to 102 μmol/l and eventually decreased further to preoperative values (figure 1).

DISCUSSION

This case report describes a patient with subacute kidney injury due to hypothyroidism after thyroidectomy awaiting ablation therapy with radioactive iodide, which seemed fully reversible after initiation of thyroid hormone substitution.

The relationship between hypothyroidism and elevated creatinine was first described in 1957. Since then, several observational studies and case series have summarized the biochemical abnormalities that occur with hypothyroidism, and their reversibility after initiation of hormone replacement therapy. Through PubMed, MEDLINE was

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**Figure 1.** The course of creatinine and TSH over time in the period following thyroidectomy

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Simsek et al. Renal injury in hypothyroidism.
Table 1. Literature overview of prospective studies evaluating changes in renal function in overt hypothyroidism

<table>
<thead>
<tr>
<th>N</th>
<th>Inclusion</th>
<th>Renal function estimation method</th>
<th>Estimated renal function in hypothyroidism</th>
<th>Estimated renal function in euthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montenegro et al. 1996&lt;sup&gt;10&lt;/sup&gt;</td>
<td>41 Primary hypothyroidism</td>
<td>eGFR (24-hour urine collection)</td>
<td>62 ± 4 (ml/min)</td>
<td>90 ± 3 (ml/min)*</td>
</tr>
<tr>
<td>Villabona et al. 1999&lt;sup&gt;9&lt;/sup&gt;</td>
<td>15 Primary hypothyroidism</td>
<td><strong>CR-EDTA clearance</strong></td>
<td>99.7 ± 3.2 (ml/min)</td>
<td>125.7 ± 41.2 (ml/min)*</td>
</tr>
<tr>
<td>Kreisman et al. 1999&lt;sup&gt;8&lt;/sup&gt;</td>
<td>24 THW in DTC</td>
<td>Serum creatinine</td>
<td>103 (μmol/l)</td>
<td>76 (μmol/l)*†</td>
</tr>
<tr>
<td>Karanikas et al. 2004&lt;sup&gt;7&lt;/sup&gt;</td>
<td>27 THW in DTC</td>
<td><strong>CR-EDTA clearance</strong></td>
<td>61 ± 18 (ml/min)</td>
<td>75 ± 23 (ml/min)*</td>
</tr>
<tr>
<td>den Hollander et al. 2005&lt;sup&gt;11&lt;/sup&gt;</td>
<td>37 Autoimmune hypothyroidism</td>
<td>eGFR (MDRD formula)</td>
<td>70 ± 17 (ml/min)</td>
<td>83 ± 24 (ml/min)*</td>
</tr>
<tr>
<td>Arora et al. 2009&lt;sup&gt;12&lt;/sup&gt;</td>
<td>46 All hypothyroidism</td>
<td>Serum creatinine</td>
<td>75 ± 4.4 (μmol/l)</td>
<td>61 ± 1.5 (μmol/l)*</td>
</tr>
<tr>
<td>Massolt et al. 2017&lt;sup&gt;5&lt;/sup&gt;</td>
<td>9 THW in DTC</td>
<td>eGFR (CKD EPI formula)</td>
<td>89.6 IQR: 69.4-93.1 (ml/min)</td>
<td>93.1 IQR: 85.8-103.8 (ml/min)*</td>
</tr>
</tbody>
</table>

THW = thyroid hormone withdrawal, DTC = differentiated thyroid carcinoma  
* Significant intra-individual change compared to values in hypothyroidism, † no SD or IQR reported, ‡ no eGFR estimation reported

searched for prospective studies evaluating the change in renal function in hypothyroidism before and after treatment with thyroid hormone. A summary of available literature is given in Table 1 including articles in English published after 1990.

These prospective studies all measured significant deterioration in renal function in consecutive hypothyroid patients, independent of the method used to estimate renal function. It has been suggested that elevated creatinine in hypothyroidism is fully attributable to increased muscle breakdown. This hypothesis is contradicted by the studies evaluating renal function through non-creatinine dependent methods<sup>5-8</sup> and studies showing elevated creatinine in the absence of substantial increase of creatine kinase.<sup>9</sup>

Nevertheless, there are multiple other mechanisms that explain the elevation of creatinine in hypothyroidism. First, hypothyroidism induces alterations in the transcription of gene products in the cardiomyocyte leading to diminished production of Ca<sup>2+</sup>-ATPase and changes in expression of phospholamban, which is a protein regulating Ca<sup>2+</sup>-ATPase activity in the sarcoplasmic reticulum of the cardiomyocyte. These alterations decrease myocyte contractility and have been shown to decrease systolic function as well as impair diastolic relaxation of the myocardium.<sup>4</sup> Second, hypothyroidism causes an increase in vascular resistance due to impaired dilatation of the endothelium.<sup>10-11</sup> The combination of these cardiovascular effects is thought to cause a decrease in renal blood flow and decrease glomerular filtration rate.

Also, renal auto regulation may be impaired by decreased sensitivity to beta adrenergic stimuli and decreased production of renin, therefore reducing the action of the renin-angiotensin system.<sup>1</sup> Finally, thyroid hormones also affect the proximal tubule in the kidney. Hypothyroidism leads to impaired water and sodium reabsorption due to decreased expression of mRNA coding for alpha and beta subunits of Na<sup>+</sup>/K<sup>+</sup>-ATPase, decreasing blood volume.<sup>12</sup> A subsequent decrease in GFR is reported, presumably caused by vasoconstriction of the afferent renal arteriole due to a tubule-glomerular feedback system response to filtrate overload.<sup>13</sup>

Although creatinine elevation is common in hypothyroidism, a near doubling of the serum creatinine as in this case was not reported in the prospective studies. However, more severe kidney injury is a rare consequence of hypothyroidism and is mostly caused by rhabdomyolysis, which has been reported as a cause in most but not all case reports.<sup>14-17</sup> Creatine kinase levels were not measured in our patient. Therefore, rhabdomyolysis cannot be excluded as the cause of acute kidney injury, although the absence of urine abnormalities does not suggest rhabdomyolysis.

In this report, due to logistic errors the duration of hypothyroidism was eight weeks, whereas a period of four weeks is recommended by the Dutch guideline. It is likely that prolonged exposure to hypothyroidism was the cause of the marked increase of creatinine. Figure 1 shows that creatinine increased linearly over time. In contrast, Karanikas<sup>9</sup> and Massolt<sup>5</sup> did not show significant further increases in serum creatinine values after five and four weeks of thyroid hormone withdrawal, compared to the two weeks of withdrawal in the study by Kreisman.<sup>9</sup>

However, the relationship between renal function and time dependent exposure to hypothyroidism has not yet been systematically studied.

Simsek et al. Renal injury in hypothyroidism.

SEPTEMBER 2018, VOL. 76, NO. 7

341
In future cases where a patient is expected to be exposed to a prolonged state of hypothyroidism (e.g. longer than the four weeks recommended by the Dutch guideline), a physician should consider expediting I-131 ablation therapy and initiation of thyroid hormone substitution or consider the use of recombinant TSH, especially in cases at risk, such as those with pre-existing chronic kidney disease. In addition, screening for hypothyroidism is recommended in cases of elevated creatinine of unknown aetiology. As a final note, even though creatinine fell back to prior values, it is important to note that a temporary deterioration of renal function has been associated with an increased risk of chronic kidney disease and mortality. Therefore, it does not seem fit to interpret such events as harmless.

In conclusion, hypothyroidism is an easily overlooked cause of renal impairment. Awareness of this phenomenon can avoid unnecessary hospital admission and costly diagnostic procedures.

DISCLOSURES

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

REFERENCES

PHOTO QUIZ

Hemothorax: a very rare complication of late diaphragmatic hernia

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CASE REPORT

A 62-year-old male presented to the emergency room with dyspnea and right upper abdominal pain for two days. He denied any trauma history. His medical history was significant for cirrhosis Child-Pugh A, chronic hepatitis B and a hepatocellular carcinoma measuring 3.3 cm in segment VII. Radiofrequency ablation (RFA) had been performed 12 months ago. On arrival, his blood pressure was 76/37 mmHg, heart rate was 110 beats per minute, oxygen saturation was 88% and temperature was 36.8 degree Celsius. On physical examination, there was tenderness over the right upper quadrant region, breathing sounds of the right lung were diminished and extremities were cold and clammy. Initial resuscitation was done. Plain radiograph revealed right pleural effusion (figure 1a).

WHAT IS YOUR DIAGNOSIS?

See page 344 for the answer to this photo quiz.

Figure 1a. Plain chest radiograph showed right massive pleural effusion.
DIAGNOSIS

Computed tomography showed massive right pleural effusion and right diaphragmatic hernia (DH) (figure 1b). The computed tomography done eight months ago showed an intact diaphragm (figure 1c). The thoracic surgeon was consulted because of suspected strangulation of the colon with septic shock. Emergency thoracotomy was performed, which disclosed a massive hemorhax caused by a serosa tear of herniated transverse colon (figure 1d). No ischemic change of the colon was noted. Both the colonic and diaphragmatic defects were repaired. The postoperative course was uneventful.

Late DH secondary to radiofrequency ablation (RFA) is an uncommon phenomenon. RFA complications are subdivided into four categories: thermal damage from heating and mechanical, septic, and other unexplained causes. The main reason for DH after RFA is diaphragmatic injury secondary to thermal damage. There are several precipitating factors, including tumor adjacent to the diaphragm, poor liver function and cirrhosis, all of which weaken the diaphragm. Early symptoms such as nausea, vomiting, and post-prandial abdominal pain are nonspecific, which makes early diagnosis difficult. When abdominal organs herniate into the pleural cavity, this may cause right upper quadrant pain, dyspnea, pleural effusion or strangulation of the bowel which in turn can result in septic shock. Diagnosis using plain radiographic examination includes visualization of abdominal organs in the chest, lack of clarity of the hemidiaphragm, or abnormal nasogastric tube positioning. Contrast-enhanced computed tomography plays an important role in the diagnosis and in determining whether the intruding abdominal organs are necrotic. Conservative treatment may be chosen in selected stable patients. Definite treatment is surgical repair, either open or laparoscopic. To prevent thermal injury induced by RFA, artificial ascites or intraabdominal carbon dioxide, insufflation before RFA to separate the hepatic tumor and diaphragm is warranted as an effective method.

In addition, hemorhax related to DH often occurs in traumatic patients. In this case, the cause of hemorhax may be related to mechanical injury from friction between the defect of the diaphragm and the herniated colon. However, most patients presenting with shock are in shock because of sepsis originating from strangulation of the bowel and not because of haemorrhage.

In conclusion, DH is a rare late complication of RFA and herniation of the colon can lead to hemorhax. Hemorhax is most often of traumatic origin. When a patient presents with shock and herniated diaphragm, the first thing to check for is sepsis; nevertheless, hypovolemic shock from hemorrhage of herniated organ should still be in the differential diagnosis.

REFERENCES


Figure 1b. Coronal CT showed diaphragmatic hernia with bowel loops (arrow), complicated by right pleural effusion
Figure 1c. Coronal CT showed intact right diaphragm (8 months before)
Figure 1d. Operation finding showed diaphragm defect (arrow) and bleeding source from serosa tears of herniated transverse colon
PHOTO QUIZ

Swelling of the breast after cosmetic augmentation

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CASE REPORT

A 48-year-old, previously healthy woman presented with an asymmetric, painless swelling of her left breast three years after cosmetic bilateral breast augmentation (McGhan, 275 gram). Blood laboratory measurements and cytological puncture showed no abnormalities. Both prostheses were removed and replaced (Sebbin, 330 gram). Six months after replacement swelling of her left breast reoccurred. MRI showed a fluid collection and intact prostheses (figure 1). Both implants were removed together with their capsules. Histology of the capsule of the left breast showed sheets of large pleomorphic cells with polymorphic nuclei at the border of seroma and capsule without infiltration of the capsule (figure 2).

WHAT IS YOUR DIAGNOSIS?

See page 346 for the answer to this photo quiz.

Figure 1. MRI scan of breast. MRI scan shows large fluid collection in left breast around implant, while the implant is intact

Figure 2. Histology of capsule (HE staining, 20x)
DIAGNOSIS

The large pleomorphic cells are positive for CD30, CD2, CD3, CD4, CD5, CD43, granzyme B, EMA and TIA1. They are negative for ALK-1, CD8, CD20, CD79a, PAX5 and CD68. The combined histological, immune phenotypical and clinical features are most consistent with the diagnosis of breast implant-associated anaplastic large-cell lymphoma (BI-ALCL), without invasion of the breast tissue. Additional positron emission tomography/computed tomography-scan and bone marrow examination showed no signs of additional lymphoma localisations.

The prevalence of women with breast implants is increasing worldwide. In 2016 the World Health Organization recognized BI-ALCL as a separate entity.\(^1\) Median time of diagnosis after implantation is 9 to 11 years. The relative risk for women with breast implants to develop BI-ALCL is 421.8 and the absolute risk is 1 per 7000 at age 75.\(^2\) Cytological analysis is the cornerstone for diagnosing BI-ALCL. The smears demonstrate large pleomorphic lymphoid cells, often with an epithelioid appearance with plenty cytoplasm and large pleomorphic, occasionally kidney-shaped nuclei with a usually prominent nucleolus. After surgical removal of the implants and capsules, histopathologic examination is mandatory to estimate infiltrative growth. Lymphoma cells are mostly confined to the seroma fluid, without invasion of the capsule and the adjacent tissues.\(^2\) BI-ALCL cells are CD30 positive and ALK-1 negative whereas ALK-1 is expressed in more than half of systemic ALCL cases. In addition, tumor cells frequently express EMA, CD2, CD3, CD4, CD43 and CD45 and rarely express CD5, CD7 or CD8. The pathogenetic mechanism leading to the development of BI-ALCL remains to be elucidated. Some studies suggest a higher change on BI-ALCL with textured implants than with smooth implants, but they also note that the use of smooth implants is very limited.\(^3\)

Otherwise, chronic inflammation in the biofilm on the implant surface, immune response, repeated trauma of the rough implant surface and the patient’s genetic makeup are thought to be associated with the development of BI-ALCL.

After diagnosing BI-ALCL, standard lymphoma workup is recommended. Without capsule invasion, conservative management is advised, with removal of the implant and capsule, as was done in this patient.\(^3\) In advanced cases, with invasion through the capsule, systemic chemotherapy is advised, where CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) and CHOP-like treatment are the most commonly used protocols. One study showed a 100% overall survival after 18 months of follow-up in cases of non-invasive, in-situ BI-ALCL, in contrast to 52.5% in advanced, infiltrative cases.\(^4\) Our patient underwent uncomplicated surgery and will be followed regularly at the outpatient clinic. In retrospect it is likely that the swelling after the first implants was an indication for the development of BI-ALCL, although the cytological puncture showed no abnormalities.

In conclusion, BI-ALCL is recognised as new entity and with an increasing incidence of breast implants BI-ALCL should be considered when swelling of the breast occurs.

REFERENCES

PHOTO QUIZ

Ulcerated nodules of the tongue

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CASE REPORT

A 59-year-old white woman was referred to our observation for ulcers of the tongue of two months duration. Her medical history included previous Merkel cells carcinoma of the zygomatic region with lympho-nodal involvement five years earlier, which had been treated with surgery, radiotherapy and chemotherapy, and a diagnosis of systemic sarcoidosis two years later, with sub-chin nodes and pulmonary involvement, the latter left untreated as functionality tests were normal. Intraoral examination showed two ulcerated nodules of the dorsal tongue (figure 1); the lesions were painless, grew slowly, and showed positivity to toluidine-blue vital test. A PET-scan revealed two distinct solid masses of the tongue with increased signal intensity, and some little lymph nodes located at the right mandibular angle. Serum sIL-2R test was not performed. An excisional biopsy of the lesions with histological examination was performed (figure 2). No adjunctive treatment was suggested for the ulcerations.

WHAT IS YOUR DIAGNOSIS?

See page 348 for the answer to this photo quiz.

Figure 1. Clinical appearance of the ulcerated nodules of the tongue

Figure 2. Histological examination (Haematoxylin-Eosin stain, original magnification x10). Multiple non-caseating granulomas (arrows) with variable appearance from discrete to well demarcated. Also, some are confluent, and contain epithelioid macrophages and multinucleated giant cells, surrounded by a diffuse lymphocytic infiltrate.
DIAGNOSIS

Sarcoidosis remains a rare disease with an unknown aetiology. Clinically, the most common presentation is pulmonary infiltration associated with hilar lymphadenopathy, usually causing fatigue, malaise, dyspnoea or weight loss. Apart from the lungs, all other organs can be involved, leading to hepato-splenomegaly, uveitis, photophobia, osteolytic bone lesions, lupus pernio and erythema nodosum in the skin, arithmias, congestive heart failure and parotitis (Heerfordt’s syndrome). The diagnosis is based upon clinical history, pulmonary function tests, haematological tests, biochemical investigations (liver and renal function tests, serum calcium, and serum angiotensin converting enzyme levels), chest radiograms and histological studies. Biopsy of the tissues involved is mandatory for the diagnosis, showing non-caseating granulomas, usually containing epithelioid macrophages surrounded by a rim of lymphocytes. These findings are not specific for sarcoidosis and detectable in other granulomatous disorders. Nevertheless, such findings should raise the suspicion of sarcoidosis and lead to further investigation. Oral involvement in sarcoidosis is uncommon; clinically, swellings or nodules, ulcers, gingivitis or gingival hyperplasia might be present. Also, jawbones can be involved, showing lytic lesions usually associated with loss of teeth, pain and swelling. The oral mucosa is the most commonly affected site, followed by gingiva, lips, floor of the mouth/sublingual gland, palate and salivary glands. Parotid gland involvement, usually bilateral, occurs in less than 10% of patients with sarcoidosis, and tongue involvement is also rare. Lesions are most often nodular, while ulceration is very unusual and can lead to misdiagnosis of malignancies.

The differential diagnosis of oral sarcoidosis includes orofacial granulomatosis, such as bacterial infections (tuberculosis, syphilis, cat-scratch disease and leprosy), fungal infections (histoplasmosis, coccidioidomycosis), foreign body granulomas and Crohn’s disease.

REFERENCES

Dear editor
With keen interest I read the newsworthy article of Fanoy et al. about the general practitioners’ skill and Q fever hospitalisation risks, recently published in the Netherlands Journal of Medicine. The authors emphasized the role of trained primary care health workers in the early diagnosis and proper management of patients with Q fever, to reduce unnecessary hospitalisation. This zoonosis mainly occurs through inhalation or ingestion of infected particles, specifically urine, feces, milk, or vaginal mucus from mammals infected with *Coxiella burnetii*. Invertebrate hosts like ticks and amoebae may also harbour this agent in human environments. Acute infections by *C. burnetii* may be asymptomatic (20-80%) or manifest themselves by fever, flu-like symptoms, pneumonia or hepatitis. Chronic manifestations are uncommon (1-5%) and include endocarditis, arteritis, pericarditis, osteoarthritis, and lymphadenitis. Outbreaks in the Netherlands confirmed the potential public health burden of this zoonosis, the role of small ruminants and the significance of the number of unsuspected chronic infections. The Dutch consensus gave rise to new diagnostic criteria for chronic Q fever. Proven cases are defined by positive tests for *C. burnetii* and endocarditis or vascular infections. Worthy of note, vascular involvement of Q fever is more often diagnosed in this region, where the hospitalisation rate of patients presenting with acute infection is approximately 2-5%. The authors highlighted the need for disseminating epidemiological, diagnostic and management updates among general practitioners, to reduce the hospitalisation of patients with Q fever. The median duration of hospitalisation was seven days, with a mean diagnostic delay of 29 days; however, prior experience, higher awareness, and more rapid tests can change this situation. Fanoy et al.’s original study is indeed a major contribution with respect to public health concerns in high income countries, but the following remarks may somehow be appropriate.

The primary course of Q fever is often asymptomatic and misdiagnosis is frequent. For these reasons, early detection of the disease and prevention of long-term complications are challenging tasks. This zoonosis mimics and can be related to endocarditis and large or medium sized arteritis, so these should be ruled out in cases with clinical suspicion of giant cell or Takayasu's arteritis. Q fever is a reportable disease and *C. burnetii* is classified as a potential bioterrorism agent. In areas with a high burden of disease, vaccination of farmers, veterinary and slaughterhouse workers may be useful, after screening the antibodies to prevent strong immune reactions. Equipment including N95 respiratory protection is indicated in laboratories and with autopsies. Consensual diagnostic and management protocols for Q fever are lacking worldwide.

DISCLOSURES

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