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The Journal of Medicine

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Editorial office
Academic Medical Centre,
Department of Medicine (E2-126)
Meibergdreef 9
1105 AZ Amsterdam
The Netherlands
Tel.: +31 (0)20-566 21 71
Fax: +31 (0)20-691 96 58
E-mail: m.m.levi@amc.uva.nl
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Contents

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EDITORIAL

In the land of double-blind studies the case report is king

M. Levi

Department of Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands, m.m.levi@amc.uva.nl

Scientific journals publish a myriad of various articles, of which reports of original scientific findings and review articles often represent the backbone of the journal. In addition, opinion-based articles, hypothesis papers, editorials, letters and rebuttals, news and views, and many other article types may be published. A particular type of paper that is typically seen in medical journals only is the case report. The case report is a popular item for many medical authors and represents about 10-15% of indexed papers in PubMed. In a case report doctors report about their observations in a particular patient or a small series of patients. Reasons for publishing a case report may vary but include the situation in which doctors are impressed by a certain patient presentation and/or clinical course, the authors' conviction that colleagues need to be informed about a specific clinical situation or development, and initial reports on new insights into pathogenesis, a novel diagnostic technique or an innovative therapeutic option. Also the case reports published in the Netherlands Journal of Medicine fall into these categories. For example, in recent years we have published interesting new aetiological or pathophysiological findings,[1,2] new diagnostic or laboratory techniques,[3] original clinical manifestations of diseases,[4,5] or new adverse events of treatment.[6-8]

There are also a number of downsides to case reports that are frequently mentioned. In the first place, case reports are anecdotes and illustrations, and their narratives may represent coincidences rather than a real significant trend that helps in understanding disease or improving diagnostic or therapeutic management. In particular case reports describing the coincidental occurrence of two different diseases are not very helpful. If an individual patient with chronic ulcerative colitis develops glioblastoma multiforme, it is quite likely that this is a coincidence rather than pointing to a genuine connection between the two diseases. Nevertheless, case reports like this are very often submitted to journals and sometimes even published. Secondly, there is a marked publication bias associated with case reports: only impressive or interesting situations are likely to be reported. Lastly, the lack of a control group or situation makes it very hard to adequately assess the true importance and relevance of any individual observation. As an example, the publication history of a recombinant activated coagulation factor to combat massive blood loss can be taken. This intervention showed highly impressive and almost immediate effects in arresting blood loss in some patients with uncontrollable haemorrhage in whom all other options had failed. The medical literature was barraged with an extreme number of case reports and case series reporting successful application of this treatment. Patients in whom this therapy failed were almost never reported, underscoring the publication bias this type of articles may have. For many years the number of patients reported in case reports exceeded the number of patients included in clinical trials and for a long time this has hampered a proper assessment of the true efficacy and safety of this intervention.[9]

Despite these disadvantages some authors argue that case reports can also have merit in some areas. Vandenbroucke argues that case reports, when clearly focused, are often crucial in detecting novelty and may therefore be instrumental in stimulating medical progress.[10] This notion was confirmed by another report demonstrating that novel observations in case reports were often followed up by subsequent clinical trials and could therefore be considered to be important hypothesis-generating reports.[11]

The undiminished popularity of case reports is underlined by the number of submissions to the Netherlands Journal of Medicine (*table 1*) and this ever increasing number of submissions does lead to a decreasing chance of acceptance.[12] In the Journal the editorial policy is to be restrictive about case reports (and basically limit acceptance to those cases that really report novel ideas or findings) and to publish interesting and illustrative examples of disease in the photo quiz section. In fact, the photo quizzes are highly popular items in the Journal and

Table 1. *Number of submissions and acceptance rate of case reports and photo quizzes in the Netherlands Journal of Medicine*

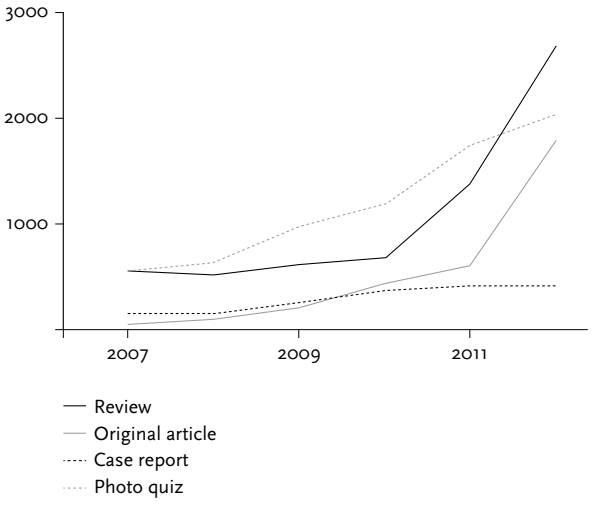
Year	Submitted case reports	Accepted case reports	Submitted photo quizzes	Accepted photo quizzes
2009	136	14%	50	68%
2010	272	11%	71	56%
2011	284	9%	63	63%
2012	372	7%	141	35%

Table 2. *Most frequently downloaded photo quizzes in the Netherlands Journal of Medicine*

Photo quiz	Number of downloads*
Smit TT, et al. An odd looking man[13]	2714
Martens H, et al. A 'chigsaw' puzzle after a vacation in Brazil[14]	2408
Tummers-de Lind, et al. Nodules on the tongue and thick lips[15]	2298
Lu H, et al. Pythons and a palmar rash[16]	2282
van Durme CM, et al. Dripping candle wax[17]	2168

***Downloads within one year of publication.**

Figure 1. *Downloads of articles*



Annual mean number of downloads of several article types in the Netherlands Journal of Medicine from the Journal's website (open access).

belong to the most frequently downloaded articles on our website (*figure 1*). The five most frequently downloaded photo quizzes are shown in *table 2*.

The case report is often regarded as a less valuable contribution to the medical literature; however, it is still widely popular among authors and probably also among readers. Hence, this publication form is likely to stay in our journals for many years to come.

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REVIEW

Guideline adherence for empirical treatment of pneumonia and patient outcome

Treating pneumonia in the Netherlands

S.M. Huijts[1*], C.H. van Werkhoven[1], W.G. Boersma[2], J. Buijs[3], G. Buunk[4], C.J. Compaijen[5], L.J.R. van Elden[6], J.E.H. Gisolf[7], R. van der Kamp[8], J.A.J.W. Kluytmans[9], B.A.F. Kuipers[10], J.J. Mager[11], B. Oppedijk[12], F. Palmen[13], J.M. Prins[14], B. van Reemst[15], M.H. Silbermann[16], F.H. van Tiel[17], E. van der Wall[18], T.S. van der Werf[19], M.J.M. Bonten[20]

[1]Julius Center for Health Sciences and Primary Care, UMC Utrecht, [2]Pulmonary Diseases, Medical Centre Alkmaar, Alkmaar, [3]Department of Internal Medicine, Atrium Medical Center, Heerlen, [4]Department of Internal Medicine, Franciscus Hospital, Roosendaal, [5]Department of Internal Medicine, Kennemer Gasthuis, Haarlem, [6]Pulmonary Diseases, Diakonessenhuis Utrecht, [7]Department of Internal Medicine, Rijnstate Hospital, Arnhem, [8]Pulmonary Diseases, Hofpoort Hospital, Woerden, [9]Laboratory for Microbiology and Infection Control, Amphia Hospital, Breda/ Oosterhout, [10]Pulmonary Diseases, Isala Klinieken, Zwolle, [11]Pulmonary Diseases, St. Antonius Hospital, Utrecht, [12]Pulmonary Diseases, Lievensberg Hospital, Bergen op Zoom, [13]Pulmonary Diseases, St. Elisabeth Hospital/ Tweesteden Hospital, Tilburg, [14]Department of Internal Medicine, Division of Infectious Diseases, Academic Medical Center, Amsterdam, [15]Pulmonary Diseases, Martini Hospital, Groningen, [16]Department of Internal Medicine, Tergooi Hospitals, Blaricum, [17]Department of Microbiology, Maastricht UMC, Maastricht, [18]Pulmonary Diseases, Spaarne Hospital, Hoofddorp, [19]Internal Medicine, Pulmonary Diseases & Tuberculosis, UMC Groningen, University of Groningen, [20]Department of Medical Microbiology, University Medical Center Utrecht and Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, *corresponding author: tel.: +31 (0)88 -755555; fax: + 31 (0)88 7555132; e-mail: s.m.huijts@umcutrecht.nl

ABSTRACT

Introduction: According to the Dutch guidelines, severity of community acquired pneumonia (CAP) (mild, moderate-severe, severe) should be based on either PSI, CURB65 or a 'pragmatic' classification. In the last mentioned, the type of ward of admission, as decided by the treating physician, is used as classifier: no hospital admission is mild, admission to a general ward is moderate-severe and admission to an intensive care unit (ICU) is severe CAP. Empiric antibiotic recommendations for each severity class are uniform. We investigated, in 23 hospitals, which of the three classification systems empirical treatment of CAP best adhered to, and whether a too narrow spectrum coverage (according to each of the systems) was associated with a poor patient outcome (in-hospital mortality or need for ICU admission).

Patients and methods: Prospective observational study in 23 hospitals.

Results: 271 (26%) of 1047 patients with CAP confirmed by X-ray were categorised in the same severity class with all three classification methods. Proportions of patients receiving guideline-adherent antibiotics were 62.9% (95% CI 60.0-65.8%) for the pragmatic, 43.1% (95% CI 40.1-46.1%) for PSI and 30.5% (95% CI 27.8-33.3%) for CURB65 classification. 'Under-treatment' based on the pragmatic classification was associated with a trend towards poor clinical outcome, but no such trend was apparent for the other two scoring systems.

Conclusions: Concordance between three CAP severity classification systems was low, implying large heterogeneity in antibiotic treatment for CAP patients. Empirical treatment appeared most adherent to the pragmatic classification. Non-adherence to treatment recommendations based on the PSI and CURB65 was not associated with a poor clinical outcome.

KEYWORDS

Antibiotic treatment, antimicrobial treatment, community acquired pneumonia, guideline adherence, patient outcome

INTRODUCTION

Ideally, antibiotic treatment of community acquired pneumonia (CAP) should be directed against the causative pathogen, but history taking, physical examination, clinical symptoms and radiological features are not reliable for predicting aetiology.[1-3] Moreover, aetiology remains unknown in 25-45% of CAP episodes.[4-6] Because of these diagnostic uncertainties it is widely recommended to use the clinical severity of CAP as guidance for empirical therapy; more severe cases should be treated with a broader spectrum of antibiotic coverage. Guideline recommendations for antibiotic treatment, though, must carefully balance between achieving appropriate empirical treatment (especially in severely ill patients) and avoiding inappropriate antibiotic use, as this will augment antibiotic resistance development and adverse events.[7]

The guidelines for the treatment of CAP issued by the Dutch Working Group on Antibiotic Policy distinguish three levels of clinical severity (mild, moderate-severe and severe) with specific recommendations for empirical treatment for each severity class.[8] For instance, oral therapy with doxycycline (or amoxicillin as alternative) is recommended for patients with mild CAP and one of three options is recommended for patients with severe CAP (*table 1*). A critical point in using these guidelines is the definition for the different severity classes, especially for severe CAP. The guidelines provide three sets of definitions, without prioritising any: the PSI score;[9] the CURB65;[10] and a pragmatic score (mild is when the patient is treated as an outpatient, moderate-severe is when hospitalised on non-ICU wards and severe CAP when admitted to the ICU, without criteria to define ICU admission). The classification system used is at the discretion of treating physicians. The aims of this prospective observational study were to monitor – without treatment dictated by study protocol – current daily clinical practice of empirical antibiotic treatment of patients with CAP in 23 hospitals across the Netherlands, to determine consistency of daily practice with the three systems for severity classification offered by the Dutch guidelines for empirical CAP management and, finally, to determine, for each of the three options, whether non-adherence was associated with clinical outcome.

Table 1. *Dutch (2005) guidelines for treatment of community acquired pneumonia*

Severity of CAP	Treatment Dutch guidelines
Mild	Amoxicillin or doxycycline
Moderate-severe	
• Negative or no Legionella test	β-lactam monotherapy
• Positive Legionella test	Macrolide or quinolone monotherapy
Severe	Moxifloxacin monotherapy OR penicillin & ciprofloxacin OR penicillin & macrolide OR cephalosporin & macrolide

MATERIALS AND METHODS

Patients

We conducted a prospective, observational, cohort study in 23 Dutch hospitals (four academic hospitals, 15 teaching hospitals and four non-teaching hospitals), between January 2008 and April 2009. Adult patients, 18 years or older, with a clinical suspicion of CAP or lower respiratory tract infection (LRTI) presenting to the emergency department or admitted to one of the participating hospitals were eligible, but only patients with 'confirmed' CAP were included in the analysis. A clinical suspicion of CAP or LRTI was defined as the presence of at least two of the following criteria: fever or hypothermia, cough or change in chronic coughing pattern, dyspnoea or tachypnoea or hypoxia, findings with percussion or auscultation consistent with pneumonia, leucocytosis or leukopenia or left shift or an infiltrate on the chest X-ray. Exclusion criteria were recent hospitalisation (<14 days) or residing in a nursing home; known anatomical bronchial obstruction; history of post-obstructive pneumonia, primary lung cancer or another malignancy metastatic to the lungs; AIDS; known or suspected P*neumocystis jirovecii* pneumonia or tuberculosis; inability to give consent; not being hospitalised. The study was approved by all local Research Ethics Committees and written informed consent was obtained from all participants.

Data collection

All data were collected in standardised case record forms by trained research nurses and/or physicians in every hospital. Antibiotic therapy was not dictated by protocol and choices of empirical antibiotic therapy were made by attending physicians only. Data collected included antibiotic use (last two weeks before admission and empirical treatment), physical examination, biochemical and haematological blood tests, chest X-ray, microbiological test results, ICU admission and/or intubation at any moment during hospital stay and all-cause in-hospital mortality.

Definitions of determinants and outcome

'Confirmed' CAP was defined as the presence of an infiltrate on the chest X-ray within 48 hours after admission together with at least two of the following signs

or symptoms: (increased) cough, sputum production, temperature >38°C or <36.1°C, auscultatory findings consistent with pneumonia, leucocytosis (>10.0 x 10^9 WBC/l) or leukopenia (<4.5 x 10^9 WBC/l), C reactive protein more than three times the upper limit of normal, hypoxaemia with pO_2<60 mmHg while the patient is breathing room air or dyspnoea/ tachypnoea.

For all three severity classification methods (PSI, CURB65 and pragmatic) all subjects were assigned to 'under-treatment', 'compliant treatment' or 'over-treatment' according to the Dutch guidelines.[8] Treatment compliant to the guidelines is summarised in *table 1*. In patients categorised as moderate-severe CAP without evidence of *Legionella* infection (negative urinary antigen test or test not performed) β-lactam monotherapy is recommended, which included all penicillins, β-lactam antibiotics with clavulanate, cephalosporins, as well as combinations of two β-lactam antibiotics. Antibiotic therapy was considered to be 'under-treatment' if the regimen covered a narrower spectrum than the Dutch guidelines advised, and therapy was considered to be 'over-treatment' if the spectrum was broader than recommended. ICU admission during hospital stay was determined only for patients who were initially admitted to a general ward.

Data analysis

The SPSS statistical package (version 20.0, SPSS Inc, Chicago, IL, USA) was used for the statistical analysis. Missing data of continuous variables included in the PSI or CURB65 score were imputed by regression methods (age, systolic blood pressure, temperature, pulse frequency, arterial pH, blood urea nitrogen, sodium, glucose, haematocrit and O_2 saturation), for the arterial pH 19.8% of the values had to be imputed and for O_2 saturation 9.1%, all other imputed values had no more than 6.0% missing values. With the imputed data the PSI and CURB65 scores were calculated.

To evaluate associations between guideline compliance and patient outcome, 'under-treatment' was compared with patients with 'over-treatment' or guideline-compliant treatment. Associations between 'in-hospital mortality' and guideline-compliant empirical treatment were evaluated by calculating crude odds ratios (ORs) first, followed by adjusted ORs after including severity of disease (based on PSI score) in a multivariate logistic regression model. PSI was included as a continuous variable in the model to limit the degrees of freedom. Subjects for whom no PSI score was calculated – the subjects in PSI class I – were assumed to have a PSI score of zero. Multivariate analyses were performed for all three classification methods (PSI, CURB65 and pragmatic). The same analyses were repeated for the endpoints ICU admission during hospital stay and the composite endpoint (in-hospital mortality or ICU admission).

RESULTS

Study population

In all, 1758 patients with a clinical suspicion of CAP were included, of whom 557 failed to meet the criteria for CAP (552 had no infiltrate on chest X-ray within 48 hours after admission and five did not meet other criteria) and 69 patients had one or more exclusion criteria. Of the 1132 patients with confirmed CAP, information on antibiotic use was missing from 33 patients and 52 patients were not admitted. So, the study population included 1047 hospitalised patients with confirmed CAP (*figure 1*). The median age of this population was 70 years (IQR 58-79), 62.8% were male, and 30.2% received antibiotic treatment before admission and 6.6% died during admission.

Empirical antibiotic therapy

Most patients (62.9%) received β-lactam monotherapy as initial treatment and 254 (24.3%) received combination treatment of β-lactams and quinolones (*table 2*).

Figure 1. *Patient flowchart*

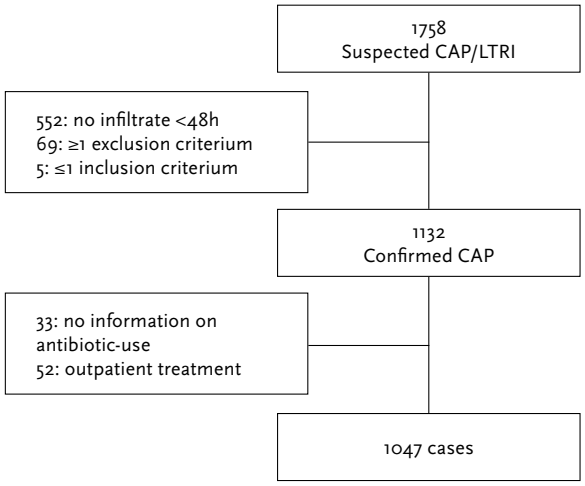

Table 2. *Empirical antibiotics in patients with CAP (n=1044)*

	β-lactam	Macrolide	Quinolone	Tetracycline	Other
β-lactam	659 (62.9%)				
Macrolide	27 (2.6%)	14 (1.3%)			
Quinolone	254 (24.3%)	3 (0.3%)	42 (4.0%)		
Tetracycline	1 (0.1%)	-	-	14 (1.3%)	
Other	18 (1.7%)	-	2 (0.2%)	-	10 (1.0%)

Three patients, not included in the table, received a combination of three antibiotics as empirical treatment.

There are marked differences in the numbers of patients assigned to each of the severity classes according to the three classification schemes. For instance, only 33 patients (3%) were considered severe CAP based on the pragmatic classification, as compared with 131 (12.5%) and 226 (21.6%) when using the PSI or CURB65 classification, respectively (*table 3*). As our analysis was restricted to hospitalised patients, no patients with mild CAP according to the pragmatic classification were included. Only 271 patients (26%) were categorised in the same severity class for all three different classification methods, of which 261 had moderate-severe and ten had severe CAP.

Antibiotic therapy was most compliant to guideline recommendations based on the pragmatic severity classification: 62.9% (95% CI 60.0-65.8%) as compared with 43.1% (95% CI 40.1-46.1%) and 30.5% (95% CI 27.8-33.3%) when based on the PSI and CURB65 classifications, respectively (*table 3*). 'Under-treatment' occurred most frequently in patients with 'severe' CAP, and was mainly due to β-lactam monotherapy. Proportions of 'under-treatment' were 8.9% (n=92) based on PSI classification, 13.8% (n=144) based on CURB65 classification and 3% (n=31) based on the pragmatic classification. In the PSI and CURB65 classification systems, 90% (n=83) and 93% (n=135) of episodes of 'under-treatment' occurred in patients with severe CAP, as compared with 35% (n=11) of 'under-treatment' episodes in the pragmatic classification system.

Adherence to guidelines and clinical outcome

Data on all-cause in-hospital mortality were available for 1036 subjects, of whom 69 (6.7%) died. Based on the PSI classification the crude OR for in-hospital mortality of 'under-treatment' was 3.70 (95% CI 2.01-6.79), but this association disappeared when adjusting for the severity of CAP (*table 4*). A similar result was found for the CURB65 classification. Comparable observations were made for the need for ICU admission and the combined endpoint. When using the pragmatic classification, adjustment for severity of CAP hardly changed ORs. However, no significant association was found.

'Under-treatment' could be misclassified in patients with severe CAP in whom coverage of *Legionella* was omitted because of negative results of the *Legionella* antigen test, known at the time of antibiotic prescription. There were 49, 101 and 18 patients with a negative *Legionella* urine antigen test on the day of admission and with severe CAP according to the PSI, CURB and pragmatic classification, respectively. If all these episodes were counted as 'correct treatment' instead of 'under-treatment' the adjusted OR for the combined endpoint would be 2.68 (95% CI 1.04-6.94) for the pragmatic classification. For the other severity classifications crude and adjusted ORs for outcome remained largely unchanged compared with the ORs (data not shown).

DISCUSSION

This observational study demonstrates that clinical use of three proposed severity classifications for CAP (based on PSI, CURB65 and a pragmatic approach) as currently recommended in the Dutch guidelines results in large heterogeneity in severity classification, with a level of concordance for classifying CAP severity as low as 26%. Adherence to antibiotic recommendations for each of these classifications will lead to markedly different antibiotic usage. The current practice as observed in this multicentre

Table 3. *Spectrum of empirical antibiotic treatment according to severity of disease classification systems; compliant treatment is considered adherent to guideline recommendations*

Severity of CAP		Antibiotic treatment according to guideline						
		Under-treatment	% of class	Compliant treatment	% of class	Over-treatment	% of class	Total
PSI	Mild	0	0.0	39	13.0	261	87.0	300
	Moderate-severe	9	1.5	389	63.1	218	35.4	616
	Severe	83	63.4	23	17.6	25	19.0	131
	Total	92	8.9	451	43.1	504	48.1	1047
CURB65	Mild	0	0.0	51	10.6	430	89.4	481
	Moderate-severe	9	2.6	230	67.6	101	29.7	340
	Severe	135	59.7	38	16.8	53	23.5	226
	Total	144	13.8	319	30.5	584	55.7	1047
Pragmatic	Mild	-	-	-	-	-	-	-
	Moderate-severe	20	2.0	648	63.9	346	34.1	1014
	Severe	11	33.3	11	33.3	11	33.3	33
	Total	31	3.0	659	62.9	357	34.1	1047

Table 4. *Associations between 'under-treatment' and patient outcome according to severity classification*

Clinical outcome		PSI	CURB65	Pragmatic
Hospital mortality (n=1036, 69 died)				
	N with under-treatment	89	143	31
	Crude OR	3.70 (2.01-6.79)	2.58 (1.47-4.53)	2.14 (0.73-6.31)
	Adjusted* OR	0.77 (0.37-1.61)	1.06 (0.57-1.98)	1.90 (0.59-6.06)
ICU admission (n=1013, 67 ICU)				
	N with under-treatment	88	140	21
	Crude OR	2.50 (1.28-4.87)	1.72 (0.93-3.19)	2.42 (0.69-8.42)
	Adjusted* OR	1.06 (0.49-2.29)	1.02 (0.52-1.97)	2.71 (0.76-9.72)
Combined endpoint (n=1035, 112 endpoints)				
	N with under-treatment	89	143	31
	Crude OR	3.60 (2.15-6.04)	2.21 (1.38-3.55)	2.50 (1.05-5.94)
	Adjusted* OR	1.09 (0.59-2.02)	1.07 (0.64-1.81)	2.38 (0.94-6.03)

OR = odds ratio. *Adjusted for severity of disease, based on PSI score.

study was most adherent to recommendations based on the pragmatic score (62.9% concordance) and least adherent to recommendations based on CURB65 (30.5%). Under-treatment based on the pragmatic classification was associated with a trend to increased risks of either ICU admission or in-hospital mortality (adjusted OR 2.38 (95% CI 0.94-6.03)).

The Dutch guidelines for CAP differ from other guidelines. The Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines use a pragmatic classification (outpatient, non-ICU inpatient and ICU inpatient) with separate recommendations for outpatients with comorbidities.[11] The British Thoracic Society (BTS) guidelines use the CURB65 score in combination with clinical judgement.[12] The Dutch guidelines are a mixture of the IDSA/ATS and BTS guidelines, as any of three classification systems (PSI, CURB65 or pragmatic classification) is recommended, without advising one in particular. Obviously, the three methods for severity classification are not unambiguous. Furthermore, Dutch guidelines still recommend β-lactam monotherapy for patients with moderate-severe CAP, where most other guidelines advise combination therapy in these patients. The clinical effects of these different guideline recommendations have never been prospectively determined.

The existence of three possible classification systems seriously complicates the analysis of guideline adherence and quantification of the clinical effects of using either of these systems if their use is not randomised. In the current study only 271 of 1047 patients (26%) were categorised in the same severity class with all three classification methods. The rationale of using severity of disease classification for choosing empirical treatment is that 'under-treatment' reduces clinical outcome, and that 'over-treatment' induces unnecessary antibiotic use. In the current study no such association could be demonstrated between 'under-treatment' based on the PSI and CURB65 classification and poor clinical outcome. Yet, for 'under-treatment' based on the pragmatic system a strong trend towards poor clinical outcome was apparent. Achieving better adherence to the PSI and CURB65-based algorithms would, therefore, increase the use of broad-spectrum antibiotics, although 'under-treatment' had no determinable detrimental effects on patient outcome.

Associations between guideline adherence and patient outcome have been studied before, but not in Dutch patient cohorts.[13-24] The results of these studies are inconsistent, which might result from differences in study design and data analysis: in some studies guideline-compliant therapy was compared with non-compliant therapy (defined as either over- or under-treatment), some evaluated compliance to guidelines not available at the time of patient inclusion or to guidelines from another country, and some only performed univariate analyses of associations.[15,16,22,24] Our findings illustrate the importance of adjustment for disease severity in such analyses.

Naturally, there are limitations to this non-experimental study. During the study period the 2005 Dutch guidelines were used, which were revised recently.[25] The major change in the new guidelines is the preference of amoxicillin above doxycycline for patients with mild CAP, which was the other way around before. Applying this change to the current data would not influence the results. Secondly the pragmatic classification might be influenced by subjective assessment, as clinical decisions to admit patients to the ICU may differ per hospital, may depend on availability of ICU beds and may be guided by restrictions in treatment ambitions, and this also applies to ICU admission after treatment failure. This information was not available and could not, therefore, be included in our analysis. Due to logistical reasons, not all

consecutive patients were included. If treatment decisions were influenced by the timing of admission, this could have influenced our findings, but we are not aware of this happening. Furthermore, there were some missing data for which imputation was used, and there were no data on 30-day mortality or causes of death, and, therefore, all-cause in-hospital mortality was used. Obviously, this may lead to misclassification if patients die shortly after hospital discharge. Finally, there were no data collected about reasons to deviate from the guidelines, such as pregnancy, allergies or previous culture results.

The strengths of our study include the large number of patients included, allowing a robust model to determine associations between 'under-treatment' and patient outcome, its multicentre design, which increases the generalisability, its prospective nature, maximising reliable and complete data collection, and, its relatively short study period, excluding changes in guideline recommendations and clinical practice. Our findings demonstrate that currently decisions for empiric antibiotic prescription coincide best with a pragmatic risk assessment. This leads to high proportions of patients who are receiving 'under-treatment' according to the more objective risk classifications based on PSI and CURB65. Yet, this 'under-treatment' according to PSI and CURB65 was not associated with a poor clinical outcome. Only 3% of all patients received 'under-treatment' according to the pragmatic risk assessment, and there was a strong tendency that this was associated with poor outcome. This provides a clear target to improve the outcome of patients hospitalised with CAP, by improving antibiotic prescription in a small proportion of patients.

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REVIEW

Head and neck paragangliomas

I.M. Werter*, C. Rustemeijer

Department of Internal Medicine, Amstelland Hospital, Amstelveen, the Netherlands, *corresponding author: tel.: +31 (0)6-20254740, fax: +31 (0)20-7556179, e-mail: inge_werter@hotmail.com
Both authors contributed equally to the manuscript

ABSTRACT

Head and neck paragangliomas (HNPGL) are rare, slowly growing tumours, presenting as a painless mass in the neck. Multiple genetic mutations are associated with HNPGL; screening can have an important role in patients of a young age and/or with a positive family history and/or malignant HNPGL. The choice of treatment should be made individually, based on the patient's condition, the risk of complications and the aim of therapy. Observation can be a logical choice given the low incidence of malignancy. In the case of intervention, surgery and radiotherapy show comparable results for local control. For definitive eradication, surgery would be the treatment of choice, involving however high risks of complications.

KEYWORDS

Paraganglioma, carotid body tumour, SDHD, radiotherapy, genetic testing

INTRODUCTION

Paragangliomas (PGL) are rare tumours arising from neural crest cells associated with autonomic ganglia along the sympathetic trunk. A small percentage of PGL are located in the head/neck region. Of PGL in the head/neck region, 65% are located in the carotid body; these are called carotid body tumours (CBT). PGL are mostly benign, slowly growing tumours and were first described by Von Haller in 1743.[1-3] They are also known as chemodectomas, because they act directly as chemoreceptors or by the secretion of catecholamines in response to stress.
Head and neck paragangliomas (HNPGL) are an important differential diagnosis for a mass in the neck region. During the last decade, more has been discovered about genetic mutations in HNPGL. Also, therapeutic regimens have been altered over the years. Hence we present two cases and give an overview on current concepts of HNPGL.

CASE 1

In our outpatient clinic a 48-year-old man, with no past medical history, presented with a painless, slowly progressive mass on the left side of the neck, which had been there for two months. He reported no other symptoms. A cousin had been treated for CBT. On physical examination we found a solid mass of 3-4 cm on the left side of the neck. Ultrasound and later magnetic resonance imaging (MRI) of the neck showed a CBT along the left side of the carotid bifurcation (*figure 1*). Urine analysis demonstrated no excess of metanephrines. The CBT

Figure 1. *MRI neck: CBT on the left side of the carotid bifurcation*

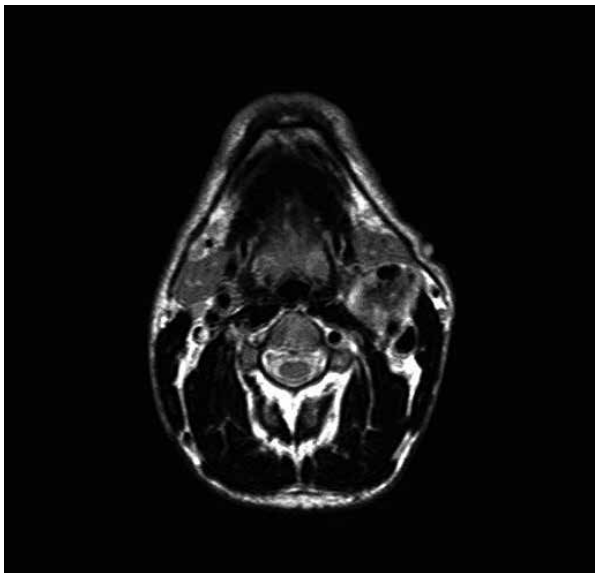
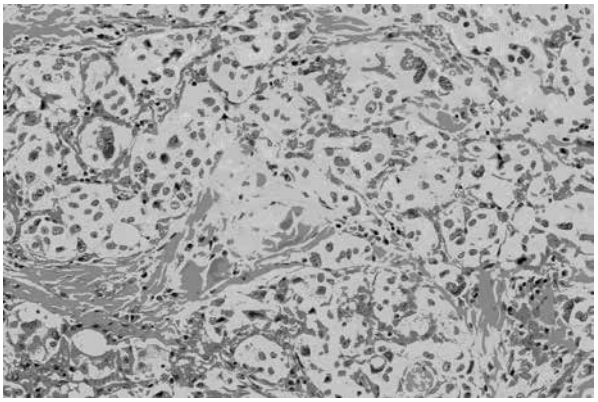


Figure 2. *Histology CBT: Organoid growth pattern of the tumour cells with an intervening stromal component and supporting sustentacular cell population at the periphery of the cell nests ('zellballen'). (Pathologist Dr. H.H. van Boven, Netherlands Cancer Institute, Antoni van Leeuwenhoek)*

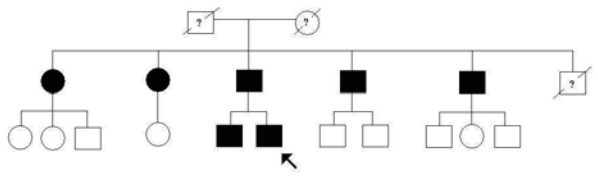


was surgically removed without complications. Typical histopathological images of CBT were seen (*figure 2*). Genetic evaluation is in progress.

CASE 2

Another man, aged 46 years, who was remotely related to the first patient, presented to the outpatient clinic with a mass on the left side of the neck; he had no past medical history and a positive family history for PGL (*figure 3*). MRI proved the mass to be a CBT (3.5-4 cm) along the left side of the carotid bifurcation, which was surgically removed. A small PGL along the right jugular artery was left in situ. Two years later the patient returned with complaints of a dystrophic tongue, caused by a PGL in the left jugular foramen, for which he received gamma knife therapy. During follow-up, more PGL evolved, namely one along the glomus tympanicum dextra (12 x 6 mm), two along the right side of the vagal glomus (24 x 7 mm and 28 x 20 mm) and one along the left side of the vagal glomus (36 x 18 mm). These HNPGL were all observed over time. Genetic evaluation of this patient and his relatives is in progress. Notably, during follow-up a prolactinoma was diagnosed on the left side of the pituitary gland.

Figure 3. *Family tree of patient 2*



CLINICAL PICTURE

Patients with HNPGL typically present at the age of 40-70 years with a gradually enlarging mass in the neck; 84% of HNPGL are painless. Sometimes hoarseness, dysphagia, and more seldom vertigo and coughing may occur, resulting from pressure on the vagus nerve or sympathetic nerves. Some patients present with hypertension, sweating and headache, due to vasoactive catecholamines produced by HNPGL.[1,4]

HNPGL are more prevalent in women than in men (1-5:1).[3,4] They grow less than 1-2 mm per year and malignancy occurs in less than 5% of the cases. However, for malignant HNPGL, ten-year survival is less than 50%.[2,5] The differential diagnosis of a mass in the neck other than HNPGL includes lymph node pathology, thyroid gland pathology, saliva gland pathology, neurofibromas and carotid artery aneurysms.

AETIOLOGY

There are two known forms of HNPGL, the sporadic form and the familial form. Thirty-five percent of all HNPGL are familial.[3] It is thought that the sporadic form is triggered by hypoxia. Research has shown that patients living at high altitude, and therefore enduring a more or less chronic form of hypoxia, have a larger carotid body.[6]

The familial form of HNPGL is less strongly related to hypoxia and more strongly associated with genetic mutations. Genetic mutations can also occur spontaneously; however, most patients with genetic mutations have a positive family history. For example, a study done in the United Kingdom found a prevalence of genetic mutations of 92% in patients with a positive family history.[7] Penetration of genetic mutations and existence of environmental factors (such as hypoxia) predispose to the development of HNPGL.

Several genetic mutations are known to be associated with HNPGL, namely SDHB, SDHC, SDHD, VHL, NF-1, RET, TMEM127, SDHAF, SDHA, MAX.[7] Generally, HNPGL are associated with mutations in the succinate dehydrogenate complex (SDH) subunit B and D (SDHB and SDHD). SDH is an enzyme complex, bound to the inner membrane of the mitochondria. Frequency of mutations is variable among different populations. For example, in the UK 27% of HNPGL have a detectable mutation in SDHB and 35% in SDHD.[7] While in the Netherlands 87% of genetic mutations in HNPGL are SDHD. The dominance of SDHD mutations is unique to the Netherlands. Altogether 88.8% of the Dutch HNPGL SDH mutation carriers have one of six Dutch founder mutations in SDHD, SDHB or SDHAF2 (SDHAF2 c.232G>A, SDHB c.423+1G>A SDHB

c.201-4429_287-933del, SDHD c.274G>T SDHD c.416T>C p.Leu139Pro SDHD c.284T>C).[8]

In patients with HNPGL, the chances of finding a genetic mutation are higher in patients with a positive family history, multiple paragangliomas, malignant disease and patients of a younger age. The median age of genetic HNPGL is 38.5 years versus 62 years in non-genetic HNPGL.[7,8] Of the described genetic mutations, SDHB is most strongly associated with metastatic disease.[9] In addition to HNPGL, a variety of other tumour types have been reported to be associated, or potentially associated, with *SDHB* or *SDHD* mutations. Case 2 described an HNPGL and a concurrent prolactinoma. To our knowledge there is only one other case published and it has not yet been associated with genetic mutations.[7]

Given the strong association of genetic mutations in HNPGL with a positive family history, occurrence of multiple tumours and young age, screening might be useful in these patients. A German study by Erlic *et al.* proposed an algorithm for genetic testing.[10] However, given the variable mutations in different populations, genetic screening should be adjusted to the population under study. This might lead to a specific Dutch screening program for the six founder genes in selected (high-risk) HNPGL patients.

DIAGNOSIS

The first step in evaluating a mass in the neck is Doppler ultrasound. If clinical suspicion of HNPGL exists, further imaging of the tumour and its relation to environmental structures is necessary. Both computer tomography (CT) and MRI are valuable methods for this purpose and can sometimes be used complimentarily. CT provides more information on bone destruction by the HNPGL than MRI, while MRI provides more detailed information about the relation of the HNPGL with surrounding vascular and bone structures. If surgery is considered, angiography remains the golden standard to evaluate the vasculature of the HNPGL.[4,11] Lastly, research has been done to evaluate position emission tomography (PET)/MRI for imaging of HNPGL. However PET/MRI is a costly and difficult technique and further research is needed to evaluate the use of PET/MRI in the diagnostic evaluation of HNPGL.[12]

Imaging techniques of HNPGL are highly specific; therefore, biopsy is not necessary to confirm the diagnosis and is relatively contraindicated because of a high risk of haemorrhage on the biopsy site. Moreover, based on histology, it is difficult to differentiate between benign and malignant HNPGL.[3] The best proof of malignancy is radiological evidence of metastatic spread.

TREATMENT

Several treatment modalities are available for HNPGL: observation, surgery and radiotherapy. As mentioned before, small HNPGL are often very slow growing and rarely demonstrate to be malignant.[2,5] Therefore, small (<3 cm), asymptomatic HNPGL can be observed over time. For elderly patients with bilateral tumours and/or a high surgical risk, observation is probably also the best policy. For large and/or symptomatic tumours surgery or radiotherapy is indicated.

Historically, surgical resection was the treatment of choice. Surgery offers a good prognosis and chances of recurrence or metastatic spread are very low. However, there are high risks associated with surgery of HNPGL, including haemorrhage, cerebral ischaemic events and cranial nerve damage.[13] The complication rate can be reduced by performing embolisation within 48 hours before surgery.[13-16] However, embolisation can provoke thrombosis. Despite embolisation, surgery for large HNPGL is still significantly associated with high risks.

Radiotherapy is an interesting option if patients have a high surgical risk, if a large lesion is unresectable or if a large haemorrhage is anticipated. There is increasing evidence that radiotherapy gives comparable prognostic results to surgery, without the risk of surgery-associated complications. Observational studies demonstrate long-term control rates (defined as stable disease or partial regression with no evidence of growth) for HNPGL of 95-96%.[17,18] Given the rarity of the condition, there are no randomised controlled trials yet to compare surgery with radiotherapy for HNPGL.

CONCLUSION

HNPGL are rare, slowly growing tumours, presenting as a painless mass in the neck. Multiple genetic mutations are associated with HNPGL, screening can have an important role in patients of young age and/or with a positive family history and/or malignant HNPGL. The choice of treatment modality should be made individually, based on the patient's condition, the risk of complications and the aim of therapy. Observation can be a logical policy, given the low incidence of malignancy. In the case of an intervention, surgery and radiotherapy show comparable results for local control. For definitive eradication, surgery is the treatment of choice, however associated with high risks of complications.

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REVIEW

Intestinal pseudo-obstruction as a complication of paragangliomas: case report and literature review

T.E. Osinga[1], M.N. Kerstens[2], M.M. van der Klauw[1], J.J. Koornstra[2], B.H.R. Wolffenbuttel[1], T.P. Links[1], A.N.A. van der Horst-Schrivers[1]*

Department of [1]Endocrinology and Metabolic Diseases, [2]Gastroenterology and Hepatology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands, *corresponding author: tel.: +31 (0)50-3613962, fax: +31 (0)50-3619392, e-mail: a.n.a.van.der.horst@umcg.nl

ABSTRACT

Intestinal pseudo-obstruction is a rare and relatively unknown complication of phaeochromocytoma/paraganglioma (PCC/PGL). Its pathophysiology can be explained by the hypersecretion of catecholamines, which may reduce the peristaltic activity of the gastrointestinal tract. Clinically, this can result in chronic constipation, intestinal pseudo-obstruction or even intestinal perforation.

We conducted a comprehensive literature search and retrieved 34 cases of pseudo-obstruction caused by either benign or malignant PCC/PGL. We also included a case from our centre that has not been described earlier. We conclude that intestinal pseudo-obstruction is a rare but potentially life-threatening complication of PCC/PGL. Intravenous administration of phentolamine is the most frequently described treatment when surgical resection of the PCC/PGL is not feasible.

KEYWORDS

Intestinal pseudo-obstruction, paraganglioma, phaeochromocytoma, treatment

INTRODUCTION

Phaeochromocytomas (PCC) and paragangliomas (PGL) are rare catecholamine-secreting neuroendocrine tumours arising from chromaffin cells of the adrenal medulla or extra-adrenal paraganglia, respectively. The release of catecholamines may lead to typical symptoms and signs such as paroxysmal headache, perspiration, pallor, palpitations and high blood pressure.[1] A clinical feature less well known is inhibition of the peristaltic activity of the gastrointestinal tract, which may result in chronic constipation, intestinal pseudo-obstruction or even intestinal perforation.[2,3] This complication is directly related to the hypersecretion of catecholamines, which may inhibit acetylcholine release from the parasympathetic nerve system and activate α_1-, α_2- and β_2-adrenergic receptors of the intestinal smooth muscle cells. Recently, we encountered a patient with a malignant PGL who had developed an intestinal pseudo-obstruction. Clinical experience with the management of this rare complication is very limited, and we therefore decided to conduct a comprehensive review of the literature on this subject with particular emphasis on the reported responses to the different treatments.

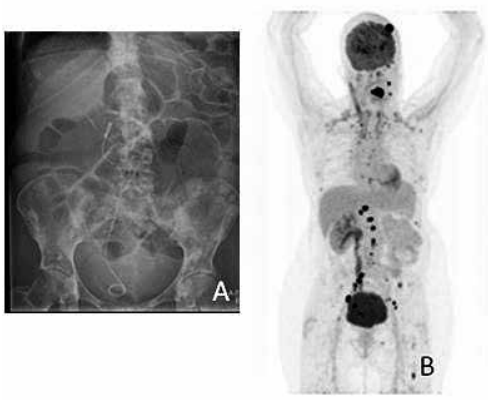
CASE

A 62-year-old female patient with a malignant PGL caused by a mutation in the succinate dehydrogenase (SDH) subunit B was admitted to our hospital with complaints of constipation and vomiting for the last three days. Her medical history included the surgical removal of a PGL of the bladder when she was 20 years of age. During this operation her left kidney was also removed because at that time a malignant epithelial tumour of the bladder was suspected. In 2009, she was admitted to the hospital because of abdominal pain and a high blood pressure of 211/145 mmHg. Further investigations revealed a

hydronephrosis due to ureteral obstruction secondary to a metastases of the PGL, which was treated by insertion of a double 'J' stent (*figure 1*). Since there were no other treatment options (peptide receptor radiation therapy with ^{111}In-octreotide or ^{131}I-metaiodobenzylguanidine (MIBG) could not be given because there was no uptake on the octreotide and ^{123}I-MIBG scan) she was treated with sunitinib from April 2011 until the time of admission described in this case report (March 2012).

Her last bowel movements had been eight days before admission. Her blood pressure and heart rate were adequately controlled with doxazosin and metoprolol. On physical examination, the abdomen was markedly distended and hypertympanic but not tender to palpation, bowel sounds were absent. The plasma metanephrine and normetanephrine concentrations were 0.24 nmol/l (reference 0.07-0.33 nmol/l) and 149.83 nmol/l (reference 0.23-1.07 nmol/l), respectively. *Figure 1* shows a plain abdominal radiograph of the patient during her hospital stay. Neither administration of laxatives or prucalopride, a selective serotonine-4 (5-HT$_4$)-receptor antagonist, resulted in any clinical improvement. Subsequently, endoscopic desufflation of the colon was performed because of an imminent risk of a blowout.[4] Colonoscopy did not reveal any mechanical cause for obstruction. Based on these findings, a diagnosis of intestinal pseudo-obstruction due to high concentrations of circulating catecholamines was considered. Oral treatment with phenoxybenzamine was started and gradually increased to a dose of 30 mg twice a day. Although this was followed by a return of bowel sounds and flatulence, there was no defecation. We therefore decided to administer metyrosine (α-methyl-L-tyrosine) in a dose of 250 mg four times a day. Subsequently, within one day the intestinal pseudo-obstruction had resolved with restoration of spontaneous defecation and disappearance of the abdominal distension. In addition, plasma normetanephrine levels were reduced to 65.01 nmol/l. Hereafter, the patient could soon be discharged from the hospital. Unfortunately, she died two months later because of progressive disease.

Figure 1. *A) Abdominal radiograph showing the colon diameter before the start of metyrosine. The maximal colon diameter measured was 12 cm. B) FDG-PET scan showing extensive lymph and bone metastasis of the paraganglioma*



REVIEW OF LITERATURE

We performed a comprehensive literature search on the clinical management of intestinal pseudo-obstruction in patients with either benign or malignant PCC/PGL. Case reports written in English, and case reports written in other languages but in Latin script were retrieved from PubMed, Embase, Web of Knowledge and Scholar Google using the following MeSH terms or text words: 'intestinal pseudo-obstruction', 'intestinal obstruction', 'Ogilvie's syndrome, 'paraganglioma' and 'phaeochromocytoma'. Data on age, gender, diagnosis, symptoms and signs, treatment and outcome were collected.

Our search yielded 32 publications, describing 34 cases (*table 1*). There was a slight preponderance of female subjects (59%), and age ranged from 25-70 years (mean 48.8 ± 13.1 years). Eighteen patients (53%) harboured a benign PCC, two patients (6%) had a benign abdominal PGL, whereas 14 patients (41%), including our own case, had a malignant PCC/ PGL. In nine patients (26%), a paralytic ileus was the initial presenting symptom at the time a diagnosis of benign PCC was made.[5-13] Among these subjects, one patient presented with a double perforation of the caecum.[6] The most frequently reported symptoms and signs were constipation (64%), abdominal pain (61%), nausea (47%), vomiting (44%), and fever (18%). On physical examination, 31 patients (91%) had abdominal distension, 17 patients (50%) had hypoactive or absent bowel sounds and abdominal tenderness was noted in 12 patients (35%). Two patients (6%) had an ischaemic bowel without signs of thromboembolic occlusion of the mesenteric vessels and five patients (15%) developed a bowel perforation. Commonly performed examinations included abdominal X-ray, computed tomography (CT) scan of the abdomen and colonoscopy. Twenty-two patients (65%) underwent adrenalectomy, of which 17 (77%) had a benign PCC. In most cases (77%) adrenalectomy was conducted after pharmacological preparation with drugs such as phentolamine, phenoxybenzamine or neostigmine and β-receptor antagonists. Nine patients (26%) were treated conservatively with either α- and/ or β-receptor antagonists or percutaneous enterogastrostomy/ enterojejunostomy or a combination of these. In one case report the drug treatment was not specified,

Table 1. *Overview of case reports reporting pseudo-obstruction or bowel perforation in patients with PCC/PGL*

Author (year of publication)	Diagnosis	Therapeutic intervention	Outcome
Zahor (1955)[43]	Malignant PCC	Resection of tumour	Died because of ventricular fibrillation just after surgery
Hughes (1962)[5]	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Bernstein (1967)[44]	Bilateral benign PCC	Phentolamine	Died after a collapse 15 hours after start phenoxybenzamine
Petrin (1967)[45]	Benign PCC	Coecostomy	Died one day after coecostomy
Korhonen (1970)[12]	Benign PCC	Died before intervention	Died because of tumour progression
Cruz (1972)[46]	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Garijo (1973)[47]	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Sznåjderman (1975)[48]	Benign PCC	Resection of tumour	Died of haemodynamic shock after surgery
Short (1976)[49]	Malignant PCC	Colostomy	Died because of tumour progression
Fisch (1976)[50]	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Turner (1983)[11]	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Thurtle (1984)[51]	Malignant PCC	Phentolamine and neostigmine; transverse colostomy	Died after surgery because of a bowel perforation
Mullen (1985)[35]	Case 1: Malignant PCC	Phenoxybenzamine, metyrosine, metoprolol	Died because of tumour progression
	Case 2: Malignant PCC	Phentolamine, phenoxybenzamine, metyrosine	Full recovery of pseudo-obstruction; FU one year
Baba (1985)[52]	Malignant PCC	Prazosin, propranolol, nifedipine	Died of tumour progression
Khafagi (1987)[7]	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Noguchi (1990)[36]	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Hashimoto (1990)[23]	Malignant PCC	Phentolamine, propranolol, midaglizole	Died of organ failure caused by tumour progression
Oliver (1990)[53]	Malignant PCC	Phentolamine	Full recovery of pseudo-obstruction
Sacks (1993)[54]	Benign PCC and HNPGL	Resection of tumour	Died of embolus 4 days after surgery
Sweeny (2000)[10]	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Salazar (2001)[9]	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Mazaki (2002)[8]	Benign PCC	Colon perforation; hemicolectomy	Full recovery; FU several visits oncologist
Sawaki (2003)[32]	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
Murakami (2003)[55]	Malignant PCC	Ileostomy	Died of tumour progression
Karri (2005)[6]	Benign PCC	Right hemicolectomy; resection of tumour	Full recovery of pseudo-obstruction
Wu (2008)[33]	Benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
De Lloyd (2010)[37]	Case 1: benign PCC	Resection of tumour	Full recovery of pseudo-obstruction
	Case 2: malignant PCC	Resection of tumour	Died 6 days after surgery because of DIS
Yamaguchi (2010)[22]	Malignant PCC	Phentolamine	Died of tumour progression and pneumonia
Edling (2011)[56]	Malignant PCC	Colectomy, ileostomy and gastrostomy tube placement	Full recovery of pseudo-obstruction
Coupe (2012)[34]	Malignant PCC	Phenoxybenzamine, β-blockade; colostomy, PEG and PEJ	Died of septicaemia four weeks after discharge
Lin (2012)[13]	Abdominal PGL	Resection of tumour	Full recovery of pseudo-obstruction
Osinga (2013)	Malignant PGL	Phenoxybenzamine, doxazosin, metyrosine	Died of tumour progression

PCC = phaeochromocytoma; FU = follow-up; HNPGL = head and neck paraganglioma; PEG = percutaneous enterogastric; PEJ = percutaneous enterojejunostomy; PGL = paraganglioma; DIS = disseminated intravascular coagulation.

and a diagnosis of phaeochromocytoma-associated intestinal pseudo-obstruction was made post-mortem.[12] Intravenous administration of phentolamine was the most frequently applied drug treatment (7 out of 9 patients; 78%). Eventually, 18 patients (53%) fully recovered from the intestinal pseudo-obstruction, whereas 16 died (47%). Causes of death were tumour progression (n=9), treatment-related complications (n=5), intestinal pseudo-obstruction (n=1), or unknown (n=1).

DISCUSSION

Intestinal pseudo-obstruction is a clinical syndrome characterised by signs and symptoms suggestive of a mechanical intestinal obstruction in the absence of a demonstrable lesion blocking the intestinal lumen. In a large series of patients with acute intestinal pseudo-obstruction, the most frequently reported clinical features were abdominal distension (100%), abdominal

pain (80%), nausea (63%) and vomiting (57%).[14] As shown in *table 2*, this syndrome may arise from several aetiologies and may present as either acute colonic pseudo-obstruction (ACPO or Ogilvie's syndrome) or chronic intestinal pseudo-obstruction.[2,14,15] The diagnosis can only be made after exclusion of mechanical obstruction or a toxic megacolon.[2,14,15] The pathogenesis of intestinal pseudo-obstruction in PGL/PCC is a direct consequence of the elevated levels of circulating catecholamines, which activate α_1, α_2 and β_2 receptors in the gastrointestinal tract. The gastrointestinal tract has its own intrinsic nervous system. This enteric nervous system is composed of two plexuses, an outer myenteric plexus and an inner submucosal plexus. The outer myenteric plexus mainly controls the gastrointestinal movements, and the inner submucosal plexus gastrointestinal secretion and local blood flow. The intrinsic activity of the enteric nervous system is modulated by the activity of the parasympathetic and sympathetic nervous system. The parasympathetic nerve endings release acetylcholine, which stimulates the activity of the plexus of the entire enteric nervous system through activation of muscarinic receptors.[16] Activation of muscarinic receptors is followed by stimulation of bowel movements, gastrointestinal secretion and blood flow. In contrast, the sympathetic nerve endings release norepinephrine, which inhibits both the plexus of the enteric nervous system through activation of the α_1-, α_2- and β_2-adrenergic receptors.[17-19] In addition, based on *in vitro* electrical recordings from the outer myenteric plexus, it has been shown that the effects of the sympathetic nervous system on the gastrointestinal tract are further augmented by a presynaptic norepinephrine-mediated inhibition of parasympathetic acetylcholine release.[16,20] Circulating epinephrine may also inhibit gastrointestinal peristaltic activity through stimulation of β_2 receptors.[3] Moreover, catecholamine-induced stimulation of the α_1 and α_2 receptors can cause vasoconstriction, which may result in intestinal ischaemia and its complications such as ischaemic colitis, necrosis and intestinal perforation.[3,6,21-23]

Table 2. *Overview of the different aetiologies of intestinal pseudo-obstruction*

Acute colonic pseudo-obstruction (Ogilvie's syndrome)[2,14]
Trauma (non-operative; e.g. fractures, burns)
Infection (pneumonia and sepsis most common)
Cardiac (myocardial infarction, heart failure)
Obstetric or gynaecological disease
Abdominal/ pelvic surgery
Neurological (Parkinson's disease, spinal cord injury, multiple sclerosis, Alzheimer's disease)
Orthopaedic surgery
Miscellaneous surgical conditions (urologic surgery, thoracic surgery, neurosurgery)
Chronic intestinal pseudo-obstruction[15]
Degenerative neuropathies (e.g. Parkinson's disease, amyloidosis, diabetes mellitus)
Paraneoplastic immune-mediated pseudo-obstruction (small cell lung cancer, carcinoid and phaeochromocytoma/ paraganglioma)
Immune-mediated pseudo-obstruction (e.g. dermatomyositis, systemic lupus erythematosus)
Infectious (Chagas' disease)
Radiotherapy/ Chemotherapy
Genetic diseases (e.g. Hirschsprung's disease)

In general, treatment of intestinal pseudo-obstruction can initially be conservative if there is no abdominal pain and if the colonic distension measured on a plain abdominal radiograph is less than 12 cm.[2,24] Conservative management includes fasting, nasogastric suction, intravenous replacement of fluids and electrolytes, and discontinuation of drugs which could adversely affect colon motility, such as narcotics and anticholinergic agents.[2,24] The risk of colonic perforation increases when the colon diameter exceeds 12 cm and when the distension has been present for more than six days.[25] Spontaneous perforation has been reported in 3-15% of patients with acute intestinal pseudo-obstruction, which carries a high mortality rate of at least 50%.[24] If conservative treatment is not successful, endoscopic desufflation or pharmacological treatment with neostigmine, a competitive acetylcholinesterase inhibitor, should be considered.[26,27] The initial response after treatment with intravenous neostigmine in patients with acute intestinal pseudo-obstruction is 89%, and in 61% of patients this response was sustainable.[27,28] Immediate surgical intervention is indicated in case of clinical signs of ischaemia or perforation.[14,29]

The incidence of PCC/PGL is low and intestinal pseudo-obstruction is an uncommon complication in this setting, as reflected by a total number of only 34 case reports in the literature, including our case. Consequently, clinical experience with the management of PCC/PGL-associated intestinal pseudo-obstruction is very limited.[30] In 26% of the cases, intestinal pseudo-obstruction was the presenting symptom of PCC/PGL. Mortality rate is high, as from this review can be concluded that 47% of patients are no longer alive within one year after development of the intestinal pseudo-obstruction. If the PCC/PGL can be resected successfully, the chances of complete recovery are high (88%).

Intravenous administration of phentolamine, a competitive α_1- and α_2-adrenergic receptor antagonist, was the most frequently applied pharmacological treatment (78%). Phentolamine inhibits α-mediated effects of catecholamines on intestinal and vascular smooth muscle cells and is usually administered preoperatively in PCC/PGL patients with drug-resistant

hypertension or a hypertensive crisis.[31] In the majority of the reported cases, treatment with phentolamine was followed by clinical improvement. However, the intestinal pseudo-obstruction often recurred after discontinuation of this drug.[7,22,23,32-37] Another limitation of phentolamine is that it can only be administered intravenously and under close haemodynamic monitoring in the intensive care unit, because of the risk of severe hypotension.[38,39] Metyrosine could be considered as an alternative treatment in PCC/PGL patients with pseudo-obstruction. Metyrosine is a tyrosine analogue that competitively inhibits tyrosine hydroxylase. This enzyme catalyses the conversion of tyrosine to dihydroxyphenylalanine (DOPA), the rate-limiting step in catecholamine biosynthesis. Metyrosine results in a depletion of the catecholamine stores inside the chromaffin tumour cells, which was also reflected by the significant decrease of plasma normetanephrine in our patient.[40,41] The use of metyrosine in patients with intestinal pseudo-obstruction might have several advantages, including oral administration without the need of blood pressure monitoring in the intensive care unit, allowing patients to use this drug at home. In clinical practice, however, the use of metyrosine is limited because of the high costs, limited availability and adverse effects in high doses.[31] Common side effects of metyrosine are sleepiness, depression, anxiety and galactorrhoea. Occasionally extrapyramidal signs may arise, because of inhibition of the catecholamine biosynthesis in the brain. Metyrosine can cause diarrhoea and crystalluria, which has been described in rats and dogs receiving 50 mg/kg metyrosine per day.[42] Although human data are scarce, patients are advised to drink approximately two litres per day.[41,42]

In conclusion, intestinal pseudo-obstruction is a rare, potentially life-threatening complication in patients with PCC/PGL as a result of high circulating levels of catecholamines. While awaiting surgery or in case curative surgery is no longer possible, treatment with catecholamine-antagonising drugs, such as phentolamine and metyrosine, or neostigmine should be considered.

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ORIGINAL ARTICLE

Incidence of hypersensitivity skin reactions in patients on full-dose low-molecular-weight heparins during pregnancy

L. Schultinge[1]*, H.M. Knol[1,2], H.C. Kluin-Nelemans[1], J.J.H.M. Erwich[2], K. Meijer[1]*

[1]Division of Haemostasis and Thrombosis, Department of Haematology, [2]Department of Obstetrics and Gynaecology, University of Groningen, University Medical Centre Groningen, the Netherlands, *corresponding authors: l.schultinge@gmail.com and k.meijer@umcg.nl

ABSTRACT

Background: Low-molecular-weight heparins (LMWH) are the most commonly used anticoagulants for the treatment and prophylaxis of venous thromboembolism in pregnancy. Hypersensitivity skin reactions associated with the use of LMWH are frequently seen, but are probably underreported.

Objective: To evaluate the incidence of hypersensitivity skin reactions due to the use of LMWH in pregnancy, and the subsequent management of anticoagulation.

Patients/methods: From 1999 to 2009, we followed consecutive women who used therapeutic anticoagulation for venous indications. Women visited a combined obstetric/coagulation clinic and were seen by a thrombosis specialist every two months until six weeks postpartum. All women were started on nadroparin.

Results: We included 135 pregnancies in 88 women. Overall, in 52 of 135 pregnancies (39%), women switched at least once to another anticoagulant because of the development of hypersensitivity skin reactions. Switching to another preparation of LMWH was effective in 77% of the cases. In 23% of the cases skin reactions recurred and another switch had to be made.

Conclusion: In almost half of the pregnancies, women had to switch at least once to another anticoagulant preparation due to the development of hypersensitivity skin reactions on LMWH. In most cases, skin reactions did not recur on the second preparation of LMWH used.

KEYWORDS

Anticoagulation, hypersensitivity skin reactions, LMWH, pregnancy, venous thromboembolism

INTRODUCTION

For pregnant women with either a current venous thromboembolism (VTE) or a high risk of recurrent VTE, low-molecular-weight heparins (LMWH) are the most commonly used anticoagulant. However, hypersensitivity skin reactions are a recognised complication in pregnant patients who use LMWH. Moreover, when this heparin intolerance occurs, alternative choices for anticoagulation are limited and hypersensitivity skin reactions might recur when another preparation of LMWH is used.[1]

A vitamin K antagonist (VKA) could be an alternative anticoagulant, but this drug crosses the placenta and its use in pregnancy is associated with significant foetal risks, particularly teratogenesis and foetal haemorrhage.[2,3] In pregnancy VKAs might also be associated with mild neurological dysfunctions in children of school age.[4] Fondaparinux is another alternative anticoagulant treatment, but data on the use in pregnancy are limited.[5]

Rates of mild hypersensitivity skin reactions due to LMWH use in the general population range from 2-7.5%.[6,7] Risk factors for the development of hypersensitivity skin reactions are female sex, obesity and long duration of heparin therapy.[7] It has been hypothesised that the hormonal status may be of influence in the pathogenesis of the delayed hypersensitivity skin reaction to LMWH.[8] Pregnancy also seems to increase the incidence of these skin reactions, ranging from 0.6-40%.[1,9-14] These reactions may present as erythematous, well-circumscribed lesions without necrosis, usually secondary to a delayed type IV hypersensitivity reaction. An urticarial rash (type I immediate hypersensitivity reaction), skin necrosis and heparin-induced thrombocytopenia have also been reported, although these types of reactions are rare.[8]

A few studies report on the incidence of hypersensitivity skin reactions to LMWH in pregnant women, but these studies had other primary outcomes and therefore hypersensitivity skin reactions are probably underreported.[9-11,13]

We performed a cohort study in our hospital to assess the safety of the use of a full dose of LMWH in pregnancy. Here, we report the prevalence of hypersensitivity skin reactions of LMWH usage during pregnancy and the subsequent management of anticoagulation.

PATIENTS AND METHODS

Patients

This is a single-centre cohort study, including 88 consecutive women who received a therapeutic dosage of LMWH during pregnancy and the puerperium. All women visited the University Medical Centre Groningen and were followed between 1999 and 2009. We included 135 ongoing pregnancies of these 88 women. Early foetal losses (<22 weeks of gestation) were not included, due to lack of information on these pregnancies. Indications for anticoagulation were a history of idiopathic, provoked or previous pregnancy-related venous thromboembolism, a VTE in the current pregnancy, recurrent foetal loss or asymptomatic severe thrombophilic defects (protein C, S or antithrombin deficiency).

Women visited a combined obstetric/coagulation clinic and were seen by a thrombosis specialist every two months until six weeks postpartum. Information on hypersensitivity skin reactions, episodes of VTE, bleeding, external risk factors for thrombosis, obstetric history, anticoagulant treatment, delivery and pregnancy outcome were collected using a standardised questionnaire and by reviewing medical records. Additional data were added retrospectively. National legislation and the ethical committee of our institution approve this type of study without the need for review of the protocol.

Treatment protocol

Women either had a prophylactic indication and were started on LMWH in early pregnancy, as soon as a pregnancy test was positive, or were treated for VTE in the current pregnancy. They were all treated with a body weight adjusted therapeutic dosage during pregnancy and until six weeks postpartum. Women with a current VTE during pregnancy were treated for six months, but at least until six weeks postpartum. Women started with a once daily dosage of LMWH, and from the 37th week of pregnancy all women switched to a twice daily dose to minimise the bleeding risk during delivery. Women were instructed about self-injection by a research nurse and received an information letter; most women actually injected themselves, but a few were injected by home-care nurses. Anti-Xa levels were not routinely measured and doses of LMWH were not adjusted for increasing bodyweight or increasing renal clearance.

Switch protocol

In the first pregnancy, all women started on nadroparin in a weight-adjusted therapeutic dosage (175 anti-Xa IU kg^{-1} day^{-1}). If a woman developed hypersensitivity skin reactions, she was switched to tinzaparin in a weight-adjusted therapeutic dosage. If the hypersensitivity skin reactions recurred again, the woman was switched to a VKA (only during the second trimester), dalteparin, danaparoid or fondaparinux. In subsequent pregnancies women started with the preparation that was used without complications during their previous pregnancy.

Definitions

The definitions were are follows:

- Red pruritic injection infiltrates: itchy, erythematous, well-circumscribed lesions without necrosis, subcutaneous, usually secondary to a delayed type IV hypersensitivity reaction.
- Generalised rash: rash not restricted to the site of injection.
- Mild symptoms: symptoms of skin reactions, (including haematomas, pruritic injection infiltrates and non-pruritic injection infiltrates) not severe enough to switch treatment (dependent on patient and doctor's preferences).

Statistical analysis

Descriptive statistics were used. The statistical analysis was performed in PASW version 18.0 (IBM SPSS, Chicago, Illinois, United States).

RESULTS

Eighty-eight women had 135 pregnancies between 1999 and 2009. Twelve of these women (=12 pregnancies) were also included in a study by Bank *et al.*[1] Median maternal age was 30 years (range 20-43). Indications for anticoagulation were previous VTE in 98 (73%) pregnancies, a current VTE in four (3%) pregnancies, an asymptomatic thrombophilic defect in 23 (17%) pregnancies and recurrent foetal loss in six (4%) pregnancies. In four (3%) pregnancies the therapeutic dosage of LMWH was given for other reasons (strong positive family history for VTE). In 66 (49%) of the pregnancies women were nulliparous. None of the patients had a history of thrombocytopenia or an allergy to LMWH. Baseline characteristics are displayed in *table 1*.

Table 1. *Baseline characteristics of study population*

Women, n	**88**
Pregnancies, n	135
Maternal age (median, range)	30 (20-43)
Parity: - Nulli- - Multi-	 66 (49%) 69 (51%)
Gestational age at delivery in weeks (median, range)	39.4 (27.5-42.3)
Birth weight in grams (median, range)	3372 (750-4890)
Indication for anticoagulation during pregnancy:	
- VTE in current pregnancy, n (%)	4 (3%)
- Previous VTE, n (%)	98 (73%)
- Asymptomatic thrombophilia, n (%)	23 (17%)
- Recurrent foetal loss, n (%)	6 (4%)
- Other (strong positive family history for VTE)	4 (3%)
Pregnancy outcome:	
- Live born	129
- Congenital birth defects	4
- Stillborn	1
- Late foetal loss (>22 weeks)	3
- Termination due to severe foetal anomalies	2

Pregnancy outcomes

The 135 pregnancies, including one twin pregnancy, resulted in 129 live infants. Median gestational age of live infants was 39.4 weeks, ranging from 27.5-42.3 weeks. Median birth weight was 3372 gram, ranging from 750-4890 gram. Three late foetal losses (23-27 weeks) were observed. In one of these three pregnancies, a VKA was used during the second trimester. In addition, one infant was stillborn due to placental abruption at 31 weeks and two pregnancies were terminated, for severe foetal anomalies (trisomy 18 and severe cardiac defect). Four live born infants had congenital defects: a cleft palate, clubfeet and a (genetic form of) retinoblastoma: no VKAs were used in these pregnancies. One male infant was born with an epispadia; in this pregnancy VKAs were used during the second trimester. Results are also displayed in *table 1*.

Anticoagulation used

Overall, in 52 out of 135 pregnancies (39%), women switched at least once to another treatment because of the development of hypersensitivity skin reactions. In 44 pregnancies (34%) women switched to another LMWH, thereafter in 77% (n=34) no other switch in treatment was required. In two pregnancies (2%) women switched twice to a different LMWH and in eight pregnancies (6%) women switched to VKA in the second trimester, due to the recurrence of hypersensitivity skin reactions. In 19 pregnancies (14%) women switched to a VKA for other reasons, such as aversion to injections or patients' preferences. In sixty-two pregnancies (46%) women continued using LMWH during their whole pregnancy and puerperium without hypersensitivity skin reactions, or with only mild reactions not severe enough to switch (*figure 1*).

Four women used danaparoid; one of these women developed a generalised rash, while one woman developed mild symptoms but continued using danaparoid.

Fondaparinux was used in 15 pregnancies (11%) because of hypersensitivity skin reactions to at least one type of LMWH in the current or previous pregnancy. No skin reactions were observed with the use of fondaparinux. These results were described elsewhere.[5]

Taking into account only the first pregnancies (n=88), all women started on nadroparin. Overall, in 37 (42%) first pregnancies, women were switched at least once to another anticoagulation treatment for hypersensitivity skin reactions. In the subsequent pregnancies, this incidence was lower: in only 13 pregnancies (28%) women were switched to another anticoagulation treatment for hypersensitivity skin reactions.

Type of skin reactions

LMWH were used in a total of 131 pregnancies. Pruritic erythematous infiltrates on the site of injection due to the use of LMWH were observed in 38% (n=50) of pregnancies. Mild symptoms which did not require a switch in treatment occurred in another 25% (n=33) of the pregnancies. Results are displayed in *table 2*.

A more generalised rash was observed in 2% (n=2) of the pregnancies. One woman developed a rash on nadroparin; no complications were observed with the subsequent use of dalteparin. Another woman developed a generalised rash on nadroparin, dalteparin and even on danaparoid. Finally, the delivery was initiated and in the next pregnancy she received VKA and fondaparinux without complications.

DISCUSSION

In this study, we evaluated the use of a therapeutic dosage of LMWH during pregnancy. Overall, in 39% of the pregnancies, women had to switch at least once to another LMWH, acenocoumarol, danaparoid or fondaparinux due

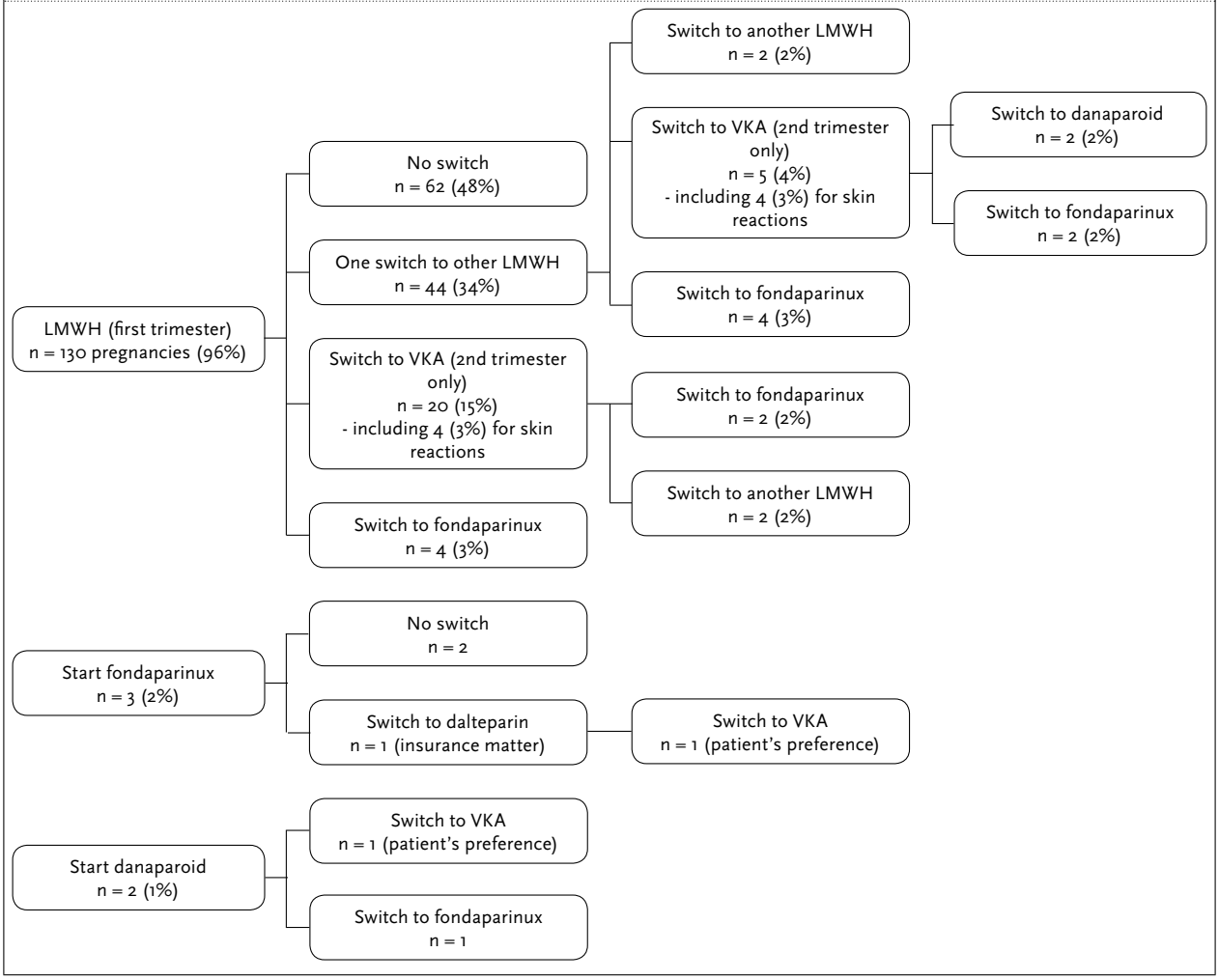
Table 2. *Reported side effects of LMWH*

	Pregnancies with exposure to LMWH (n= 131)
No side effects, n(%)	46 (35%)
Pruritic injection infiltrates, n(%)	50 (38%)
Rash (generalised), n(%)	2 (2%)
Mild symptoms, n (%)	33 (25%)

to the development of hypersensitivity skin reactions. In the first pregnancies with a full-dose anticoagulation (n=88) the rate was even higher: 42% switched at least once to another anticoagulation treatment. Switching to another preparation of LMWH seems to have a good effect, because in 77% of these pregnancies no second switch was needed.

Compared with other studies with skin lesions as primary outcome, our rate exceeds the highest reported rate of 29% by Bank *et al.*[1] They reported a prospective, observational study, including 66 pregnant women. They found a skin complication rate of 29%; these skin complications consisted of itching (20%), local redness (23%), subcutaneous infiltrates at the injection site (11%), pain during injection (3%) and a generalised rash (3%). To maintain a consecutive cohort, data of 12 pregnancies included in the study by Bank *et al.*[1] were also included in our study, but excluding these pregnancies did not change our results. Other studies that assessed the usage of LMWH during pregnancy had mostly bleeding or thrombotic complications as a primary outcome. Two reviews evaluated the complication rate of LMWH and also reported skin reactions as a secondary outcome in pregnancy. First, Sanson *et al.*[9] performed a review of 21 studies, including 486 pregnancies. They found only three cases (0.6%) of diffuse skin reactions, which led to cessation or change of treatment. Second, in a review by Greer and Nelson-Piercy,[11] 64 reports were included with in total 2777 pregnancies. They found that 1.8% of women using LMWH in pregnancy developed allergic skin reactions. We think that the high rate of skin complications we report here is real. A study by Kaandorp *et al.*[13] compared the effect of aspirin plus heparin or aspirin alone in women with recurrent miscarriage, as a secondary outcome they report that 40% of the women in the heparin group complained of swelling and local redness at the injection site. Wütschert *et al.*[8] also suggested in a review that the incidence of hypersensitivity skin reactions on LMWH might be underreported. In our hospital women were followed with a focus on adverse events, which may be an explanation for the higher incidence of reported hypersensitivity skin reactions. However, the

Figure 1. *Switches of anticoagulation treatment during pregnancy*



true percentage of hypersensitivity skin reactions in this cohort seems to be even higher, because some women did develop mild skin reactions, but did not switch to another treatment.

Different types of hypersensitivity skin reactions are described.[8,12] Most common is the delayed type IV hypersensitivity reaction; other reactions include type I immediate hypersensitivity reactions, skin necrosis and heparin-induced thrombocytopenia.[8] In our study the delayed type IV reaction was also most commonly observed.

Fondaparinux was used in 15 pregnancies in our study. No hypersensitivity skin reactions were observed, but the use of this drug is limited by the fact that it crosses the placenta.[15] The use of fondaparinux in this study population was already described elsewhere.[5]

Schindewolf *et al.*[7] described an increased risk for developing hypersensitivity skin reactions for a body mass index greater than 25, duration of heparin therapy longer than nine days and female sex. They reported an overall incidence of 7.5%, but they included only a few pregnant women. In our cohort, patients by definition had at least two of these risk factors. Unfortunately, we had no information about the BMI, so we could not analyse this relation.

A limitation of our study was the diagnosis of the skin reactions. The interpretation and the decision to switch to another anticoagulant was based on a clinical diagnosis made by different doctors, and was not objectified by skin tests. On the other hand, there is also no consensus in the literature about how to test skin allergy to LMWH.[8] A recent review by Schindewolf *et al.*[12] recommended switching to another LMWH without prior skin tests, especially in pregnant women. They advise to switch to a different heparin preparation, thus performing a subcutaneous provocation of fair sensitivity.

Because the optimal dosage of thromboprophylaxis in women with an increased risk of VTE during pregnancy and puerperium is not established, we chose to give a therapeutic dosage of LMWH to all pregnant women with an indication for thromboprophylaxis.

In our study a tendency towards more hypersensitivity skin reactions on nadroparin can be observed. Schindewolf *et al.*[14] suggested in a review that nadroparin probably had a more allergenic epitope in the nadroparin molecule than other heparins. There is a bias by indication; all women were started on nadroparin and other preparations were only used when a woman had already shown hypersensitivity skin reactions to nadroparin. Switching treatment seems to have a good effect, but we cannot exclude that longer duration of exposure to LMWH might also decrease the development of hypersensitivity skin reactions.

Our findings should lead to an altered view of hypersensitivity skin reactions during pregnancy. Physicians should be aware that patients receiving LMWH have a high risk of developing a delayed type IV hypersensitivity reaction. Therefore, we recommend monitoring pregnancies with anticoagulant treatment to recognise skin reactions.

In conclusion, we report here a 39% rate of hypersensitivity skin reactions in women on LMWH during pregnancy. These reactions can primarily be managed by changing therapy to another preparation of LMWH, which is successful in 77% of the patients. In a subgroup of women, it is necessary to ultimately switch to VKA or fondaparinux.

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CASE REPORT

Keep an eye out for tubulo-interstitial nephritis

S.A.M.E.G. Timmermans[1,2]*, J.J. Huitema[2], J.J.J.M. Wirtz[2]

[1]Maastricht University, the Netherlands, [2]Department of Internal Medicine, St. Laurentius Hospital Roermond, the Netherlands, *corresponding author: tel.: +31 (0)6-10709379, e-mail: sjoerd.timmermans@student.maastrichtuniversity.nl

ABSTRACT

Acute tubulo-interstitial nephritis and uveitis syndrome (TINU) is a rare disease, generally presenting in young women. We describe a 16-year-old Turkish girl with aspecific symptoms and elevated serum creatinine. Further, she complained about a burning pain in her left eye. Renal biopsy revealed acute TIN. Other conditions were excluded and TINU was diagnosed.

KEYWORDS

TINU syndrome, Dobrin syndrome, tubulo-interstitial nephritis, uveitis

What was known on this topic?
TINU is a rare, but treatable, disease generally presenting in young women. The diagnosis is made by exclusion.

What does this add?
Search for deteriorating renal function in patients with uveitis is required, since TIN may be present subclinically. Renal outcome is favourable if treated with corticosteroids. Relapsing uveitis or ocular manifestations can occur after years, thus ophthalmological follow-up is warranted.

INTRODUCTION

Acute tubulo-interstitial nephritis (TIN) is an important cause of acute kidney injury (AKI). Fifteen percent of biopsies for evaluating AKI reveal TIN.[1] The concomitant presentation of TIN and uveitis is an uncommon clinical entity, known as TIN and uveitis syndrome (TINU; also known as the Dobrin syndrome).[2] The diagnosis is of importance, since uveitis can persist or recur for over ten years, whereas renal disease is often self-limiting.[3] However, establishing a diagnosis of TINU may be particularly difficult in some cases, because both manifestations may not occur concurrently. Here, we describe a 16-year-old patient presenting with aspecific symptoms and elevated serum creatinine, in whom a diagnosis of TINU was made.

CASE PRESENTATION

A 16-year-old Turkish woman was admitted to our hospital because of renal impairment. She had been well until three weeks earlier, when her general practitioner prescribed amoxicillin/clavulanic acid because of a urinary tract infection. Thereafter, nausea, vomiting, fatigue, and anorexia developed. The anorexia was associated with a 6 kg weight loss within a two-week period. The patient did not have dysuria, haematuria, a decrease in urine output, or kidney pain. Neither skin lesions nor arthralgia were observed.

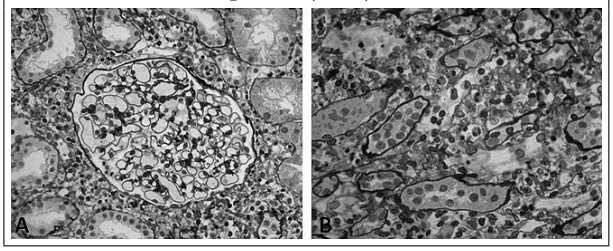
The patient was not critically ill. On examination, no abnormalities were found with the exception of a tender abdomen on palpation. The blood pressure was 117/70 mmHg, pulse 101 beats/min, and temperature 38.1°C. Laboratory tests showed normochromic normocytic anaemia, thrombocytosis, and an increased C-reactive protein (114 mg/l). The white blood cell count revealed no abnormalities. An elevated serum creatinine was found (171 μmol/l, eGFR 34 ml/min). Liver function tests, serum calcium, and protein electrophoresis were normal. Testing for antinuclear antibodies was weakly positive, whereas rheumatoid factor was negative. A urinary screen revealed proteinuria, glycosuria, and erythrocyturia. Microscopic urine analysis showed 2-5 erythrocytes and

10-25 leukocytes per high power field, leukocyte and hyaline casts. Urine and blood cultures were negative.
Ultrasonography excluded postrenal causes, whereas fluid admission did not improve renal function. Testing for antibodies to dsDNA, extractable nuclear antigens, Goodpasture's antigen, anti-neutrophil cytoplasmic antibodies and cryoglobulins was negative. The IgG subclass distribution was normal and complement levels were not reduced.
On the seventh day, she developed a burning pain in her left eye. The ophthalmologist made a diagnosis of non-granulomatous anterior uveitis. The same day, a renal biopsy revealed normal glomeruli, and an infiltrated, oedematous interstitium (*figure 1*). The infiltrate consisted mainly of plasma cells and eosinophils (*figure 1B*). Neither granulomatous lesions nor fibrosis were found. Immunofluorescence was negative. The diagnosis of TINU was made. The patient was treated with systemic and topical corticosteroids. Two weeks after therapy, her renal function and uveitis improved.

DISCUSSION

TINU has been reported in different parts of Europe. However, no cases have been reported in the Netherlands until now. This may be because physicians have been unaware of this syndrome and therefore laboratory evaluations have not been carried out in patients with uveitis and subclinical TIN. Indeed, TINU is a rare disease with a prevalence of 1-2% in tertiary uveitis centres.[4] The classic combination consists of acute TIN and uveitis. As in our case, renal manifestations precede the uveitis in 65% of cases.[5] However, TINU may be underestimated since TIN could be present subclinically in patients with isolated uveitis. Thus, it is of importance to search for systemic symptoms, i.e. fever, weight loss, fatigue, anorexia, and arthralgia. Alongside renal impairment, abnormal liver function tests, anaemia, eosinophilia, and increased erythrocyte sedimentation rate can be found.

Figure 1. *The renal biopsy represents normal glomeruli (A) and an oedematous, (lymphocytic, eosinophilic) infiltrated interstitium (B) suggestive of acute tubulo-interstitial nephritis (TIN)*



Tubular injury can present as a partial or complete Fancony syndrome. TINU is three times more common in women compared with men. Nevertheless, the incidence of the latter is increasing.[6] The mean age is 15 (9-74) years.[5]
The pathogenesis remains poorly understood, but it is thought to be the result of an autoimmune process that might involve cellular and humoral immunity. The former is considered probable since an increased soluble interleukin 2 receptor (sIL2R) level and decreased CD4/CD8 ratio have been described,[7] whereas autoantibodies directed against tubular and ocular antigens have been observed by others.[8,9] Thereby, strong associations with some HLA profiles, i.e. HLA-DRB1*0102,[10] have been reported. The precipitating factor is not known, but infectious as well as non-infectious causes, i.e. medication,[11] are being held responsible for such aberrant immune response.
Combined renal and ocular manifestations are well-known features of some aetiologies. The differential diagnosis must include sarcoidosis, Sjögren syndrome, Behçet's disease, granulomatosis with polyangiitis, systemic lupus erythematosus, rheumatoid arthritis, IgG4-related disease, and infectious diseases, such as tuberculosis. These diseases were excluded by serological testing and histopathological examination. An additive chest X-ray was performed. Neither granulomatous lesions nor bilateral lymphadenopathy were found, excluding sarcoidosis and tuberculosis. According to the diagnostic criteria,[5] a diagnosis of (definite) TINU was made.
In terms of treatment, renal function could improve spontaneously. However, systemic corticosteroid therapy (dose of 1 mg/kg/day for 2-3 weeks) is indicated in the case of progressive renal insufficiency.[12] Relapsing TIN has been described in sporadic cases, in whom a remission was induced by mycophenolate mofetil[13] or cyclosporine A.[14] Since the uveitis is located anteriorly in most cases, local treatment is preferred. Instead of TIN, relapses of the uveitis are not uncommon and seem to be lower in patients treated with systemic corticosteroids.[15] Here, the uveitis responded well to topical and systemic corticosteroid therapy. However, relapses has been described even after ten years.[3] Recurrent ocular manifestations tend to be more severe during relapses. Hence, follow-up with an ophthalmological examination is warranted. Attention must be paid to the development of diffuse vitreous opacities[15] and intraocular complications, i.e. cataract and glaucoma, since complications have been reported in 21% patients with uveitis.[5]

CONCLUSION

TINU is a rare syndrome, generally observed in young women. Male incidence, however, is increasing. In cases of

uveitis, one must search for systemic manifestations and subclinical TIN, since uveitis can present prior to acute TIN. Symptoms respond well to corticosteroid therapy. Nevertheless, ocular manifestations could occur even after long-term follow-up. Hence, ophthalmological follow-up is warranted.

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PHOTO QUIZ

Tenosynovitis of the right hand

E. Formanoy[1], H.Y. Lam[2], J.E. Arends[1]*

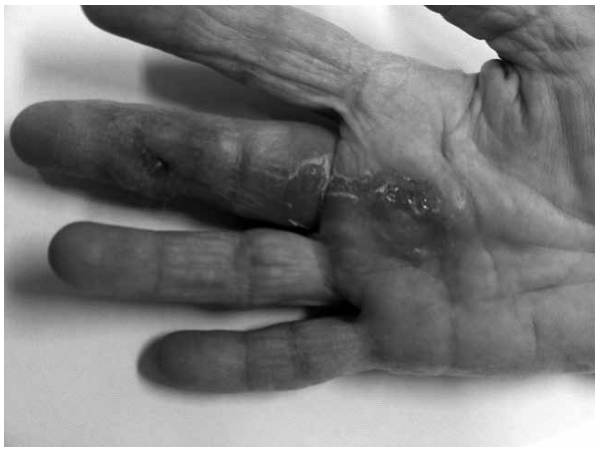
[1]Department of Internal Medicine and Infectious Diseases, University Medical Center Utrecht, Utrecht, the Netherlands, [2]Department of Dermatology, Isala Clinics, Zwolle, the Netherlands, *corresponding author: tel.: +31 (0)88-7556228, fax: +31 (0)30-2523741, e-mail: j.e.arends@umcutrecht.nl

CASE REPORT

A 64-year-old woman was seen at her general practitioner's (GP) office in April 2011 with an inflamed middle finger of the right hand. She did not recall any recent trauma or skin infection. Three months earlier she had had pneumonia and around the same time the diagnosis of rheumatic polymyalgia was made, for which she took oral prednisone 5 mg per day. She was prescribed amoxicillin, but the inflammation of the finger did not subside. Subsequently, corticosteroids were injected into the finger by her GP three times over a two-month period to treat a possible aseptic inflammation. When this therapy failed the patient was referred to a plastic surgeon, because of a ruptured flexor tendon of the inflamed finger, who referred her to our hospital for further evaluation and treatment.

At this time, the inflammation had been present for ten months. A detailed history revealed no aquarium or gardening hobby. Physical examination showed three small wounds with effusion on the right hand (*figure 1*). The finger was swollen and movement was impossible. Laboratory analysis showed: C-reactive protein 11 mg/l, erythrocyte sedimentation rate (ESR) 17 mm in first hour, normal liver enzymes, kidney function parameters, glucose, TSH and complete blood count while a blood culture was negative.

Figure 1. *Swelling and redness of the finger and palm of the right hand*



WHAT IS YOUR DIAGNOSIS?

See page 530 for the answer to this photo quiz.

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PHOTO QUIZ

The iron bowel

M. Hoogeveen[1,2,*], B. ten Tusscher[1]

[1]Department of Intensive care, VU University Medical Center, Amsterdam, the Netherlands, [2]Departement of Intensive care, Rijnland Hospital, Leiderdorp, the Netherlands, *corresponding author: e-mail: hoogeveenmascha@hotmail.com

CASE REPORT

A 53-year-old woman with a history of anorexia nervosa, laxative abuse and iron deficiency, for which she used ferrous fumarate, presented to our emergency department after intentional intoxication with benzodiazepines. She was comatose (GCS 3) and in acute respiratory distress resulting from massive aspiration with prolonged hypoxaemia before hospital admission. She was intubated and ventilated. Further examination raised the suspicion of an ileus. The plain abdominal X-ray (*figure 1*) and CT scan (*figure 2*) with only rectal contrast showed radio-opacity apparently of the bowel wall, as well as dilatation without an obstruction.

Figure 1. *Plain X-ray of the abdomen. Radio-opacity of the bowel wall mimicking intra-luminal contrast (white arrows)*

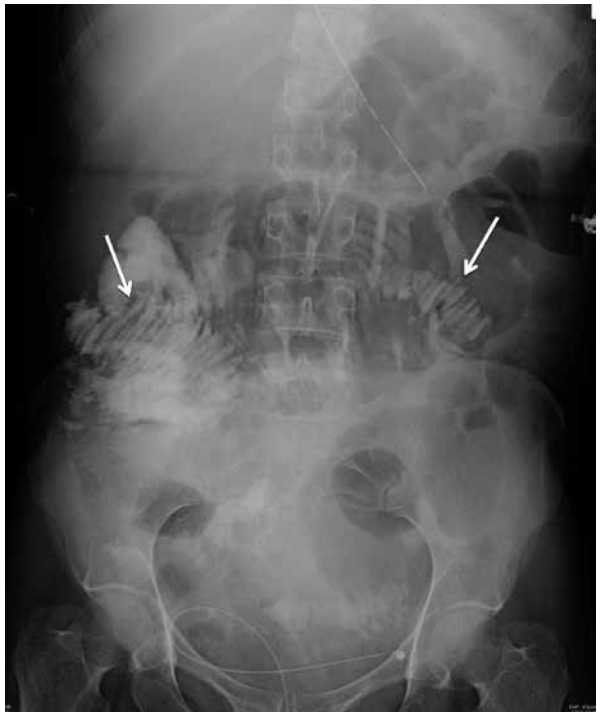
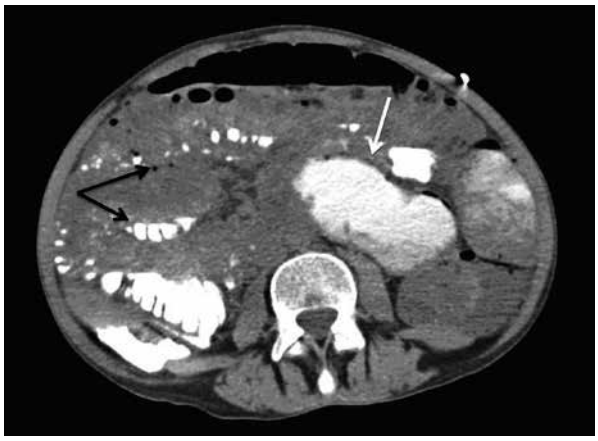


Figure 2. *Axial CT scan of the abdomen with only rectal contrast (white arrow). Radio-opacity of the bowel wall mimicking intra-luminal contrast (black arrows)*



WHAT IS YOUR DIAGNOSIS?

See page 531 for the answer to this photo quiz.

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PHOTO QUIZ

Cardiorespiratory arrest after administration of an antibiotic

A.H. Calf[1]*, E. Meijer[1], L.H. Takens[2], A.H. Hobbelt[2], W.M.T. Janssen[1]

Department of [1]Internal Medicine and [2]Cardiology, Martini Hospital, Groningen, the Netherlands, *corresponding author: tel.: +31 (0)50-5245245, fax: +31 (0)50-5245889, e-mail: agnetacalf@hotmail.com

CASE REPORT

An 82-year-old mentally retarded male presented to the emergency department with abdominal pain and dyspnoea. His medical history included volvulus for which he had undergone surgery. He did not smoke. Physical examination showed a blood pressure of 130/70 mmHg, heart rate of 95 beats/min, temperature of 39.0°C, and diffuse abdominal tenderness. The ECG was normal. Since the patient fulfilled the criteria for systemic inflammatory response syndrome and no drug allergy was known, we started intravenous administration of amoxicillin/clavulanic acid according to local guidelines before availability of laboratory results. Immediately after administration of the antibiotic, the patient experienced a cardiorespiratory arrest. The ECG recording showed ST elevation in the inferior leads and reciprocal depression in anteroseptal leads, aVR and aVL (*figure 1*). Under the suspicion of acute myocardial infarction, we started cardiac resuscitation, including administration of aspirin and heparin. After the patient was stabilised, we discovered a mild erythematous rash. Ten minutes after the administration of the antibiotic, the ECG normalised (*figure 2*).

Figure 1. *Electrocardiogram immediately after the administration of amoxicillin/clavulanic acid*

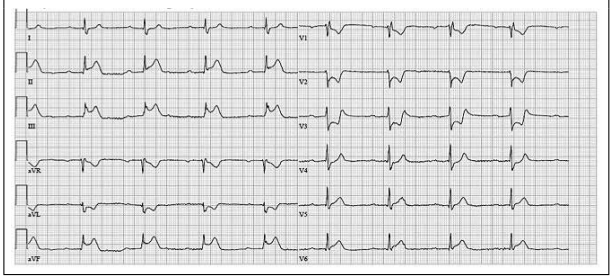
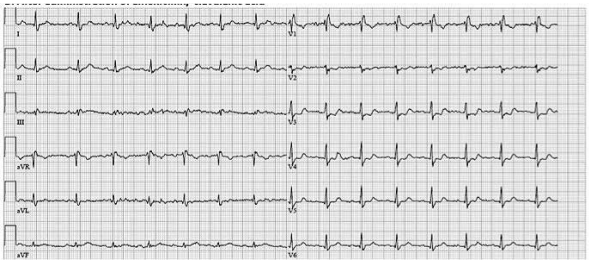


Figure 2. *Electrocardiogram ten minutes after the administration of amoxicillin/clavulanic acid*



WHAT IS YOUR DIAGNOSIS?

See page 532 for the answer to this photo quiz.

Netherlands
The Journal of Medicine

PHOTO QUIZ

Pareses, paralysis and parasites

A.P.J. Vlaar[1]*, J.W.R. Hovius[1,2], K. Stijnis[1,2], M. van Vugt[1,2]

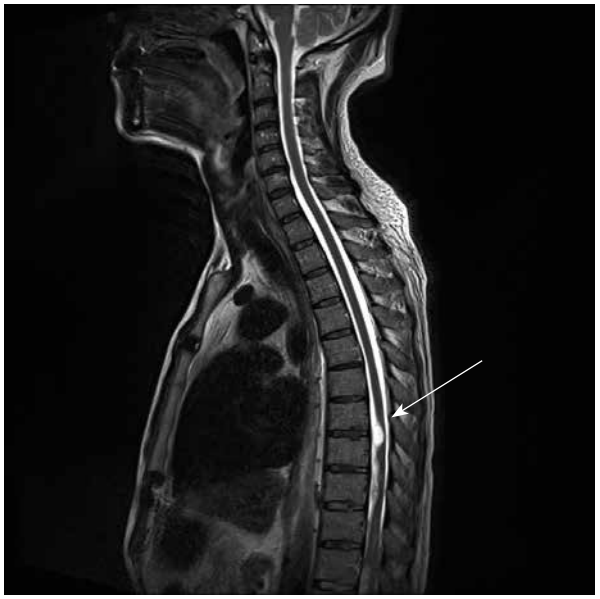
Department of [1]Internal Medicine and [2]Infectious Diseases, Academic Medical Center, Amsterdam, the Netherlands, *corresponding author: tel.: +31 (0)20-5669111, e-mail: a.p.vlaar@amc.uva.nl

CASE REPORT

A 44-year-old male of Mediterranean origin presented to our emergency department because of pareses of the lower extremities. Five years ago he underwent multiple pelvic and spinal surgical interventions in another hospital, because of cyst formation in the bone. No other organs were affected by cyst formation. Because of the pareses of the lower extremities an MRI was performed of the spine which revealed intra-spinal cysts compressing the spinal cord (*figure 1*).

The patient gave consent to have his case details and image published.

Figure 1. *MRI T2-weighted image of the cervical and thoracic spine in sagittal orientation. Intra-spinal extradural cysts with the maximum compression of the spinal cord at the level of thoracic 7 (arrow)*



WHAT IS YOUR DIAGNOSIS?

See page 533 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 526)

TENOSYNOVITIS OF THE RIGHT HAND

DIAGNOSIS

Cultures taken from the infection site revealed a *Mycobacterium kansasii*, leading to the diagnosis of a flexor tenosynovitis due to *M. kansasii*. It is the leading cause of mono-articular synovitis of non-tuberculous mycobacterium origin.[1,2] *M. kansasii* is a slow-growing non-tuberculous mycobacterium and most often causes pulmonary disease in immunocompromised patients. It is an environmental pathogen that can be found in tap water or in cattle and swine.[2]

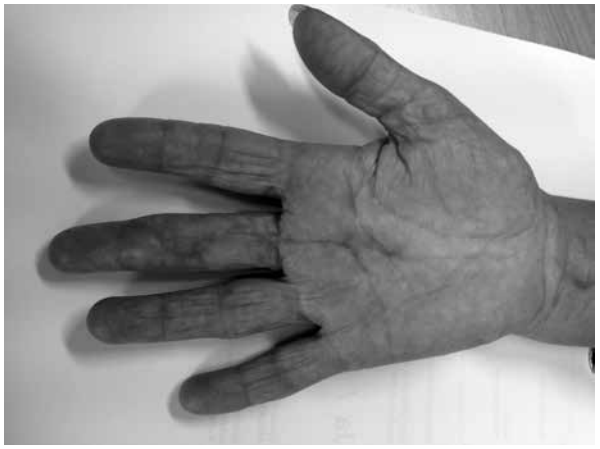
Patients with synovial infection of the hand or wrist caused by *M. kansasii* generally complain of stiffness, tingling of fingers and swelling. In most cases there is a great delay before the cause is recognised, as demonstrated by our patient, where the diagnosis was made after ten months. Moreover, corticosteroid injections are often administered before diagnosis, which can accelerate the infectious process possibly contributing to tendon damage and rupture, as seen in our patient. There is often a history of (minor) trauma to the site of infection.[3]

Diagnosis can be made with a culture from tissue taken from the infection site, but also a polymerase chain reaction (PCR) can be used to aid diagnosis since it is useful for making a rapid diagnosis.[4] When cultured and exposed to light, *M. kansasii* produces a yellow pigment, therefore the colonies can be either bright yellow (exposed) or white (not exposed).

Standard treatment of *M. kansasii* infection consists of triple therapy with rifampicin (the cornerstone), isoniazid and another anti-mycobacterial agent, often ethambutol, for 12-18 months. Shorter duration is associated with higher relapse rate. Other options for anti-mycobacterial agents are clarithromycin, and newer fluorquinolones such as moxifloxacin and linezolid.[5]

Our patient was treated with clarithromycin, rifampicin and ethambutol. Ethambutol and clarithromycin were stopped after nine months, because of side effects, and linezolid and moxifloxacin were started. After 11 months all drugs were stopped due to side effects. Tissue cultures were negative after which she underwent further reconstructive hand surgery to regain full function of her finger (*figure 2*).

Figure 2. *Right hand after complete treatment and healing of the infection, before reconstruction*



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ANSWER TO PHOTO QUIZ (PAGE 527)

THE IRON BOWEL

DIAGNOSIS

The most logical explanation would be contrast media from recent radiological imaging. However, no contrast studies had been performed in the last months. During preceding hospitalisation an upper endoscopy and a colonoscopy were done for analysis of an iron deficiency anaemia and chronic diarrhoea. The intestinal view with dark pigmentation was consistent with (pseudo) melanosis coli. Biopsies were taken, unfortunately only from the oesophagus, which showed a brown pigment in the bowel wall. In this patient, the histological picture in the oesophagus was that of ulcerative inflammation of which only the ulcer base was present in the biopsies (*figure 3*). Some undetermined brown pigment was present, since melanin staining was negative, not in line with pseudomelanosis coli. With pseudomelanosis, the brown pigment is debris and can result from chronic damage, for instance in the colon caused by chronic laxative abuse (*figure 4*). Pseudomelanosis (coli) in general does not cause opacities seen on radiological images and therefore offers no explanation for the bowel wall enhancement on the plain abdominal X-ray and CT scan as shown above.

Chronic laxative abuse can, however, result in delayed colonic transit and thereby facilitate accumulation with precipitation of ferrous fumarate in the bowel wall.[1] This is in our opinion the most likely explanation for the opacities on radiological imaging. No biopsies were obtained after iron supplement therapy commenced to support this assumption, however. Iron staining on the oesophageal biopsies was negative (not shown). Another suggestion could be precipitation of iron in the mucous layer lining the bowel lumen. This phenomenon is also encountered with much bigger materials such as radio-opacity markers.[2-4]

The patient never recovered from her comatose state due to encephalopathy as a result of periodic severe anoxia caused by massive aspiration. She died after withdrawal of life-prolonging treatment. Unfortunately post-mortem examination on the body was not permitted.

Figure 3. *Oesophagus biopsy showing fibrinoid change with active inflammation, some pigment is visible (white arrow), upper inset: Larger collection of pigment, lower inset: melanin staining negative*

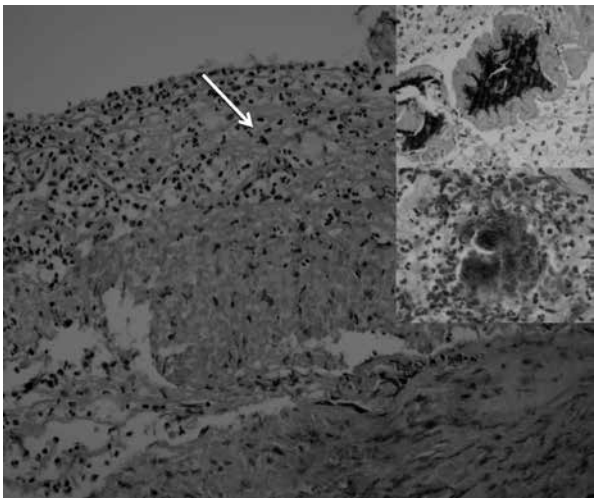
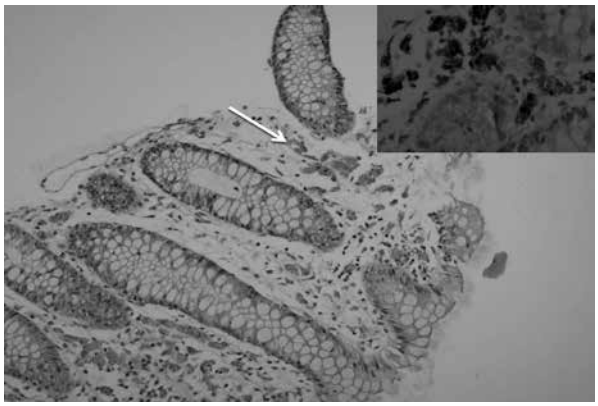


Figure 4. *Colon biopsy showing pigment (white arrow) phagocytised in macrophages within the lamina propria consistent with pseudomelanosis coli. Inset: melanin stain (Schmorl) showing positive staining*



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ANSWER TO PHOTO QUIZ (PAGE 528)

CARDIORESPIRATORY ARREST AFTER ADMINISTRATION OF AN ANTIBIOTIC

DIAGNOSIS

We suspected an allergic reaction to amoxicillin/clavulanic acid after the discovery of the rash, and administered clemastine and prednisolone. When the patient was stabilised, we excluded pulmonary and abdominal pathology by computed tomography. Coronary angiography did not show any coronary artery occlusion. We established the diagnosis of acute coronary spasm caused by an allergic reaction after the administration of β-lactam antibiotic. It is also known as the Kounis syndrome.

DISCUSSION

Kounis syndrome, or allergic angina, is a syndrome in which patients with a hypersensitivity reaction present with acute coronary syndrome. It was first described by Kounis and Zavras in 1991 and is associated with massive mast-cell degranulation during a type I allergic reaction. Mast cells release endogenous mediators, including histamine. Histamine increases cardiac contractility and heart rate, and causes vasospasms through H1 and H2 receptors. Histamine also induces tissue factor expression, which contributes to thrombus formation resulting in acute coronary occlusion.[1,2] Two variants of the Kounis syndrome have been described.[3] The first variant includes patients with normal coronary arteries without predisposing factors for coronary artery disease in which an allergic reaction induces coronary artery spasms. The second variant includes patients with culprit but quiescent pre-existing atheromatous disease. An allergic reaction can induce plaque rupture, which may result in an acute myocardial infarction.

The treatment of Kounis syndrome has two goals: 1) dilatation of the coronary vessels by vasospasmolytic agents, and 2) suppression of the allergic reaction by corticosteroids. The use of epinephrine is doubtful. It is life-saving in anaphylaxis, but it can aggravate ischaemia, prolong the QTc interval, and induce coronary vasospasms and arrhythmias.[4]

This case illustrates the potential harm of rapid antibiotic administration. Although rapid administration of antibiotics can be life-saving, physicians should carefully consider this use of antibiotics and need to be aware of the risks and adverse outcomes after administration.

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DIAGNOSIS

The current case describes a patient with *Echinococcus granulosus* infection. In our case intra-spinal cyst formation was caused either by disease progression or more likely by parasite seeding during spinal surgery in the past. *Echinococcus granulosus* infection, also referred to as hydatid cyst, is a zoonosis caused by adult or larval stages of tapeworms.[1] *E. granulosus* and *E. multilocularis* are the most common, causing cystic echinococcosis and alveolar echinococcosis, respectively. The life cycle of *Echinococcus granulosus* consists of a definitive host (dogs and other carnivores) and an intermediate host (sheep, goats, swine and humans). *Echinococcus granulosus* causes an infection in the small intestine of the definitive host and produces eggs that are passed with the host's faeces. Intermediate hosts, coincidentally also humans, ingest the infected dog's faeces. Eggs hatch into oncosphere larvae that travel through the blood and form hydatid cysts in the intermediate host tissue. In a natural environment the infected intermediate host is an easy prey for the definitive host which completes the life cycle of *Echinococcus granulosus*.

Echinococcus granulosus infection has a high prevalence in parts of Eurasia, the Russian Federation, China, Africa, Australia and South America, but is a rare zoonosis in Northern Europe and Northern America.[2] However, because of increasing movements of people around the world it has become prevalent throughout the world.

The initial phase of *Echinococcus granulosus* infection is always asymptomatic. Although almost any site in the body may be affected, either from primary inoculation or via secondary spread, the liver is affected in two-thirds of the cases. Infection of the central nervous system is rare, especially as a sole infection site. Hydatid disease of the spine occurs in 1% of all cases of human echinococcosis and is most commonly located in dorsal spine (50%) followed by lumbar (20%), sacral (20%) and cervical spine (10%).[3]

The treatment of *Echinococcus granulosus* is difficult and based on expert opinion.[2] Therapy options for bone and spine location include surgery and chemotherapy with albendazole and praziquantel.[1] Combined therapy seems to reduce the length of treatment and it is particularly recommended pre-surgery and in bony or disseminated hydatidosis.

In our case, no surgery was performed due to the disseminated form of spinal echinococcus and the high probability of new seeding of echinococcus during new surgery. During follow-up, local progression of cysts was noted. Despite long-term albendazole and praziquantel treatment there was unfortunately progression to paralysis with no further therapeutic options.

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SPECIAL ARTICLE

Women with silicone breast implants and unexplained systemic symptoms: a descriptive cohort study

M.C. Maijers[1], C.J.M. de Blok[2], F.B. Niessen[1], A.A.M. van der Veldt[3], M.J.P.F. Ritt[1], H.A.H. Winters[1], M.H.H. Kramer[3], P.W.B. Nanayakkara[3]*

[1]Department of Plastic and Reconstructive Surgery, [2]Faculty of Medicine, [3]Department of Internal Medicine, VU University Medical Center, Amsterdam, the Netherlands, *corresponding author: e-mail: P.Nanayakkara@vumc.nl

ABSTRACT

Background: Since their introduction, the safety of silicone breast implants has been under debate. Although an association with systemic diseases was never established, women continuously blamed implants for their unexplained systemic symptoms. In 2011, a pattern of symptoms caused by systemic reactions to adjuvants (e.g. vaccines, silicone) was identified: 'autoimmune syndrome induced by adjuvants' (ASIA). Our aim was to collect a cohort of women with silicone breast implants and unexplained systemic symptoms to identify a possible pattern and compare this with ASIA.

Methods: Women with silicone breast implants and unexplained systemic symptoms were invited through national media to visit a special outpatient clinic in Amsterdam. All were examined by experienced consultant physicians and interviewed. Chest X-ray and laboratory tests were performed.

Results: Between March 2012 and 2013, 80 women were included, of which 75% reported pre-existent allergies. After a symptom-free period of years, a pattern of systemic symptoms developed, which included fatigue, neurasthenia, myalgia, arthralgia and morning stiffness in more than 65% of women. All had at least two major ASIA criteria and 79% fulfilled ≥3 typical clinical ASIA manifestations. After explantation, 36 out of 52 women experienced a significant reduction of symptoms.

Conclusions: After excluding alternative explanations, a clear pattern of signs and symptoms was recognised. Most women had pre-existent allergies, suggesting that intolerance to silicone or other substances in the implants might cause their symptoms. In 69% of women, explantation of implants reduced symptoms. Therefore, physicians should recognise this pattern and consider referring patients for explantation.

KEYWORDS

Allergy, autoimmune induced adjuvant disease (ASIA), explantation; silicone breast implants, systemic symptoms

BACKGROUND

Since their introduction to the market in 1962, silicone breast implants have been the subject of international debate. From 1992 to 2006, the Food and Drug Administration (FDA) restricted the use of silicone breast implants due to controversy about their safety and concerns about their association with systemic symptoms and alleged autoimmune diseases.[1,2] Currently, over four million women worldwide have been augmented or reconstructed with silicone breast implants.[3] The vast majority of these women seem satisfied with their implants and do not experience any local or systemic symptoms.[4]

The question whether silicone breast implants can cause serious systemic health problems has often been posed but seldom thoroughly answered.[5] Local complications described are breast pain, capsular contraction, implant rupture, asymmetry, and infection.[6,7] In addition, breast implants have been associated with a very rare type of lymphoma.[8] Although often suggested,[9,10] no studies could confirm strong associations between silicone breast implants and atypical systemic symptoms or well-defined autoimmune diseases.[11,12]

Alternatively, some authors have reported a pattern of symptoms in patients with silicone breast implants that mimic autoimmune diseases.[10,13] In the early 1990s, this even led to the introduction of a new 'disease' called 'siliconosis' or 'silicone reactive disorder' with symptoms such as memory loss, fever, morning stiffness, paraesthesia, hair loss, sweating, and joint pain. These 'diseases' were

introduced by lawyers in lawsuits against breast implant manufacturers.[10,13] In 2004, a causal relationship between these symptoms and silicone breast implants was still not confirmed.[14] In 2011, immunologists, however, discovered similarities with systemic symptoms and immunological reactions to other adjuvants, such as vaccines. A syndrome called 'autoimmune (autoinflammatory) syndrome induced by adjuvants' (ASIA) was introduced and defined by several major and minor criteria (*table 1*).[15] According to two Dutch authors at least two major criteria or one major and two minor criteria are required for the diagnosis of ASIA.[16] Until now, only a few case series have reported women with silicone implants who fulfil the criteria of ASIA.[17,18]

The recent recall of silicone breast implants of the French manufacturer Poly Implant Prothèse (PIP), due to fraudulent usage of industrial silicone gel, has reignited the debate on the safety of silicone implants.[19,20] As a result, worried patients with implants from different manufacturers presented to their GPs, plastic surgeons, and other physicians with unexplained systemic symptoms. Most of these women felt ignored, as physicians tend to deny any association between silicone implants and their complaints. In addition, several of these women even went to court to get recognition for their health problems, which they believe to be caused by their silicone breast implants. Therefore, Dutch health authorities in association with the Netherlands Society of Internal Medicine and Netherlands Society of Plastic Surgery introduced a special outpatient clinic for women with silicone breast implants and unexplained systemic symptoms, which resulted in the present inventory.

Table 1. *Suggested criteria for diagnosis of ASIA*

MAJOR CRITERIA
1. Exposure to an external stimuli (infection, vaccine, silicone, adjuvant) prior to clinical manifestations.
2. The appearance of 'typical' clinical manifestations:
• Myalgia, myositis or muscle weakness
• Arthralgia and/or arthritis
• Chronic fatigue, unrefreshing sleep or sleep disturbances
• Neurological manifestations (especially associated with demyelination)
• Cognitive impairment, memory loss
• Pyrexia, dry mouth
3. Removal of inciting agent induces improvement
4. Typical biopsy of involved organs
MINOR CRITERIA
1. The appearance of autoantibodies or antibodies directed at the suspected adjuvant
2. Other clinical manifestations (i.e. irritable bowel syndrome)
3. Specific HLA (i.e. HLA DRB1, HLA DQB1)
4. Evolvement of an autoimmune disease (i.e. MS, SSc)

ASIA = autoimmune (auto inflammatory) syndrome induced by adjuvants; HLA = human leukocyte antigen; MS = multiple sclerosis; SSc = systemic sclerosis.

The aim of this descriptive cohort study was to identify a possible pattern of symptoms in a cohort of women with silicone breast implants and unexplained systemic symptoms. In addition, similarities between these symptoms and the so-called ASIA syndrome were explored.

PATIENTS AND METHODS

In December 2011, Dutch women with silicone breast implants and systemic symptoms were invited by the national media (e.g. television and internet) to attend a specialised outpatient clinic at VU University Medical Center in Amsterdam. This descriptive cohort study was approved by the Medical Ethics Review Committee of the VU University Medical Center. All women visited the clinic on their own request and none were rejected for evaluation. Women with any type of silicone breast implants were accepted. At the outpatient clinic, medical history and physical examination were performed by an experienced internist to exclude any alternative explanation for the complaints.

A detailed medical history was taken with special attention to the characteristics of the implants (e.g. type of implant, reason for implantation) and experienced symptoms (e.g. time to symptoms, local complaints, and systemic symptoms). The physical examination consisted of a general examination with special attention for breast and axillary lymph nodes. All women underwent chest X-ray (to exclude sarcoidosis) and general laboratory blood tests, including C-reactive protein (CRP), haemoglobin, thrombocytes, leucocytes with differentiation, renal function and liver enzymes. On indication, with the aim of excluding alternative explanations for their complaints, additional imaging tests and immunological serology were performed (e.g. antinuclear factor (ANF)).

After the visit to the outpatient clinic, additional data were obtained using a structured questionnaire. To this end, all women were contacted by phone and interviewed by an independent researcher. According to the questionnaire, women were asked in detail about the implantation history and self-reported symptoms.

Finally, the collected data were analysed using SPSS software (SPSS for Windows 21.0, Inc., Chicago, IL, USA 2012). For the analysis, self-reported symptoms were compared with the ASIA criteria as mentioned in *table 1*. Data are presented as median with range.

RESULTS

From March 2012 to March 2013, 84 women and two men presented to the specialised outpatient clinic. Four out

of the 84 women declined participation in the inventory. In addition, two male patients with silicone testes were excluded from the cohort. Finally, 80 women with silicone breast implants and systemic symptoms could be included in the analysis. Characteristics of these 80 women are summarised in *table 2*. The median age was 47 years (range 22-78 years). The majority of women (89%) had silicone breast implants for cosmetic reasons. The median total exposure time to silicone breast implants was 14.5 years (range 2-42 years). Although most women did not have a medical history besides breast augmentation, 60 out of 80 women (75%) reported pre-existent allergy (*table 2*) prior to implantation.

Of the 80 included women, 79% of them had local symptoms such as breast pain or capsular contraction (*table 3*). Besides local symptoms, all women reported systemic symptoms (*table 4*). The most frequently reported symptoms included fatigue (89%), neurasthenia (74%), joint pain (69%), muscle pain (65%), morning stiffness (65%), night sweats (63%), and dyspnoea (45%). In addition, women experienced cognitive problems (35%), dermatological symptoms (31%), gastrointestinal symptoms (30%), and alopecia (23%). Of note, only a minority of women reported psychological symptoms including sleeping disorders (19%) and depression (4%). While being exposed to silicone breast implants, 11 out of 80 women (14%) developed a total of 14 confirmed autoimmune diseases at a median time of seven years after first implantation (range 3-30 years; *table 5*). In the women who were not diagnosed with an autoimmune disease, routine blood tests, chest X-ray, and additional investigations did not show significant abnormalities, with the exception that ANF serology was positive in 20% of the women.

Following implantation of silicone breast implants, the women reported a symptom-free period with a median of 4.5 years (range 1 month to 30 years). In most women, the symptoms developed gradually or semi-acutely, but in 11 out of 80 women the onset of all their complaints was quite acute. Shortly before the onset of their symptoms, two women had undergone a mammography, one woman had a closed capsulotomy, and another woman had experienced a trauma with a ball on the thorax.

When classified according to the suggested ASIA criteria (*table 1*), as summarised in *table 6*, all women had at least two major ASIA criteria and 79% of the women even fulfilled ≥3 typical clinical ASIA criteria manifestations. Besides memory loss, other cognitive impairments (*table 1*) were noticed such as word finding problems, coordination and concentration problems.

Because of the unexplained symptoms a number of women decided to have the implant explanted. At the time of the analysis, 52 out of 80 women had had an explantation of

Table 2. *Characteristics of 80 women with silicone breast implants and unexplained systemic symptoms*

	n	%
Age (years)		
<30	4	5
30-40	11	14
40-50	29	36
50-60	21	26
60-70	14	18
>70	1	1
Intoxications		
Nicotine	25	31
Alcohol	45	56
Other drugs	1	1
Known allergy		
None	20	25
Metals	3	4
Food	2	2
Atopic constitution*	19	24
Medicines	14	17
Latex/rubber/plasters	3	4
Multiple	19	24
Silicone exposure (years)		
<5	4	5
5-10	15	19
10-15	21	26
15-20	13	16
20-25	8	10
>25	19	24
Implant replacements		
None	35	44
1-2	31	39
3-5	13	16
>5	1	1
Reason for implantation		
Augmentation	71	89
Reconstruction	9	11

n = number of women; % = percentage of women; *eczema, hay fever, pollen and dust mites allergy.

Table 3. *Local symptoms in 80 women with silicone breast implants and unexplained systemic symptoms*

	n	%
None	17	21
Pain	41	51
Capsular contraction	40	50
Lymphadenopathy*	28	35
Changed size, form or consistence	20	25
Lost sensibility	9	11
Infection	5	6
Local skin disorders	3	4
Rotation	1	1

n = number of women affected; % = percentage of women affected *axillary (n= 16), neck (n = 10), thoracic wall (n= 2).

Table 4. *Pattern of unexplained systemic symptoms in 80 women with silicone breast implants*

	n	%
Fatigue	71	89
Neurasthenia of the extremities*	59	74
Arthralgia**	55	69
Myalgia	52	65
Morning stiffness***	52	65
Night sweats	50	63
Dyspnoea	36	45
Cognitive problems†	28	35
Dermatological symptoms‡	25	31
Disorders of digestive tract	24	30
Alopecia	18	23

n = number of women affected; % = percentage of women; *patients described pins and needles, tingling, feeling of numbness, a heavy feeling in the extremities; **mostly in the small joints of the hands and feet; ***severe stiffness for more than 30 minutes; †word finding problems, concentration and coordination problems and memory loss; ‡rash, eczema, urticaria and itch.

Table 5. *Confirmed autoimmune disease in 11 women with silicone breast implants and unexplained systemic symptoms*

Confirmed disease*	n
Antiphospholipid syndrome	1
Scleroderma	1
Systemic lupus erythematosus	1
Sjögren's disease	2
Ulcerative colitis	1
Crohn's disease	1
Psoriatic arthritis	2
Autoimmune hepatitis	1
Perniciosa	2
Lichen sclerosis	2

n = number of women; *some women have more than one confirmed diagnosis.

Table 6. *Eighty women with silicone breast implants and a pattern of unexplained systemic symptoms according to ASIA criteria*

	n	%
MAJOR CRITERIA OF ASIA		
1. Exposure to external stimuli	80	100
2. Typical clinical manifestations		
Chronic fatigue or sleep disturbances	72	90
Neurological manifestations (demyelination)*	59	74
Arthralgia and/or arthritis	55	69
Myalgia	52	65
Cognitive impairment, memory loss**	28	35
Pyrexia, dry mouth	25	31
3. Removal of stimuli leads to improvement		
Explantation or replacement not yet done	30	38
No improvement yet***	17	21
Significant improvement	33	41
4. Typical biopsy		
Pathology not done	62	77
Silicone in lymph node	3	4
Silicone found in capsular tissue	12	15
Histiocytic reaction	3	4
MINOR CRITERIA OF ASIA		
1. The appearance of autoantibodies: ANF serology		
Unknown	10	12
Weak positive	16	20
Doubtful	11	14
Negative	43	54
2. Other clinical manifestations†	.	.
3. Specific HLA (i.e. HLA DRB1, HLA DQB1) ‡	.	.
4. Evolvement of an autoimmune disease	11	14

ASIA = autoimmune (autoinflammatory) syndrome induced by adjuvants; n = number of women affected; % = percentage of women; *neurasthenia was included; **memory loss, word finding disorders, coordination and concentration problems; ***limited follow-up; ANF = antinuclear factor; †to the authors it remains unclear which manifestations can be included; HLA = human leukocyte antigen; ‡not done.

their breast implants. Currently, the median follow-up after explantation is seven months (range 1 month to 18 years). Among the 52 women who underwent explantation, 36 women reported a significant decrease of their symptoms, whereas nine of these 36 women stated that their symptoms had completely disappeared.

DISCUSSION

The present nationwide study shows a pattern of self-reported symptoms in 80 women with silicone breast implants and unexplained symptoms, which included fatigue, muscular and joint pain, morning stiffness, neurasthenia, pulmonary, cognitive and dermatological symptoms. The observed pattern of symptoms resembled the typical clinical manifestations of ASIA.[15] All women had at least two major criteria and 79% of them had more than three typical clinical manifestations. In addition, 79% of women had local symptoms such as breast pain or capsular contraction. Furthermore, 75% of women reported a history of allergy before implantation. Because of their unexplained symptoms, 52 women decided to explant the silicone implants and 36 of these women reported significant reduction of their symptoms.

In our population, we identified a clear pattern of self-reported symptoms, which resembled a newly introduced syndrome, known as ASIA. Although most studies could not confirm an association between silicone implants and connective tissues diseases,[11,21] a few studies demonstrated an association between implants and undefined symptoms such as fatigue, arthralgia, myalgia

and cognitive symptoms.[10,22,23] In the present cohort, most women reported semi-acute onset of their symptoms, which could be explained by implant rupture or silicone gel bleeding. Previously, it has been described that symptoms of chronic fatigue, impaired short-term memory and multi-joint pain can develop after implant rupture.[24]

Besides systemic symptoms, 79% of women experienced local symptoms such as breast pain or capsular contraction, suggesting an association between local and systemic symptoms in our population. In line with these clinical observations, associations between local breast symptoms and systemic symptoms as well as immune factors have been described earlier in women with silicone breast implants. For example, capsular contraction has been demonstrated to be associated with systemic symptoms and circulating immune complexes.[25,26] Women with silicone breast implants and autoimmune diseases have shown differences in human leukocyte antigen (HLA) typing as compared with asymptomatic women with implants.[27] HLA DR and HLA DQ positive haplotypes are overrepresented in women with silicone breast implants and systemic symptoms.[13] In a recent study, it has been demonstrated that in susceptible individuals a disturbance in the modulation of key cytokines might be responsible for a perpetuation of the inflammatory reaction, which locally causes capsular contracture and systemically may trigger autoimmune diseases.[28] When left in situ, capsular tissue may continue to provoke systemic symptoms even after explantation of the silicone implants.[29]

Prior to implantation, the majority of women (75%) reported a pre-existent allergy. Silicone is generally believed to be a biologically inert product and used in many medical devices including artificial valves, joints and needles.[30] However, recent case reports have described allergy-like reactions in patients with silicone in pacemakers, nasogastric tubes and cochlear implants.[31-33] More recently, Hajdu *et al.*[34] suggested that systemic symptoms following exposure to silicone, such as described in ASIA, may only appear in subjects with underlying diseases or high susceptibility. In addition, a study in 2008 demonstrated that women with silicone breast implants had a higher serum IgE than women without silicone breast implants.[35] The results of our study subscribe to the hypothesis that silicone or other chemical substances in the implants may cause systemic symptoms in women with atopy or a hyperimmune state.

After explantation of silicone implants, 36 out of 52 women experienced a significant reduction of their symptoms. In the literature, only a few studies have described the outcome of explantations in patients with silicone implants and unexplained systemic symptoms. In several studies, recovery of these symptoms has been described after explantation, but prospective studies are lacking.[36-38] Although the follow-up of the present cohort is too limited for definite conclusions, our findings suggest that explantation may be an adequate treatment for unexplained systemic symptoms in women with silicone breast implants. As capsular tissue can function as an adjuvant itself, capsulectomy should be considered as well. Although we noticed a significant improvement in many patients after explantation these results should be interpreted with caution because there was no control group. We will continue to include patients in this cohort in the future, with the aim of following them up for at least five years. We will start using a standardised questionnaire before and after explantation to gather information on systemic symptoms prospectively.

Another potential limitation of this study is the design, as women with silicone breast implants and unexplained symptoms visited the specialised clinic on their own request, leading to selection bias. In addition, as most of the signs and symptoms were subjective, recall bias or suggestion cannot be excluded. Although, it is worth mentioning that two experienced clinicians with vast experience examined these patients looking for alternative explanations for their symptoms, before including them in the present descriptive cohort study. Since radiology investigations were not performed routinely, due to financial limitations, it was not possible to investigate the relation between silicone leakage and unexplained symptoms. As the Netherlands is a relatively small country, enabling travelling from every region to our clinic, we expected a large number of women to visit the clinic. Although women came from all over the Netherlands, only 84 women visited the clinic within 12 months. As the women had easy access to the specialised clinic and their visits were paid by the Dutch insurance companies, we believe that a representative number of women visited this clinic. As a result, we may conclude that the prevalence of unexplained systemic symptoms in women with silicone breast implants is probably low.

Although questioned for decades, the safety of these implants has not been adequately investigated. Since the PIP debacle, the importance of large prospective registration studies and post-market surveillance for medical devices has been frequently emphasised.[39,40] As long as such studies are lacking, observational and retrospective studies may provide valuable information. We realise that the present study has several limitations, but believe that our preliminary findings may help physicians, such as general practitioners, plastic surgeons and internists, to recognise this pattern of systemic symptoms in women with silicone breast implants and unexplained symptoms. Although the prevalence of this pattern appears to be low it is of significant importance to recognise these symptoms and consider explantation as the unexplained symptoms may lead to unnecessary health care consumption in women with silicone breast implants.

CONCLUSIONS

In the present descriptive cohort study in the Netherlands, the unexplained systemic symptoms in 80 women with silicone breast implants were evaluated. A clear pattern of symptoms was reported including fatigue, joint and muscle pain, morning stiffness, night sweats, cognitive and dermatological complaints. The observed pattern of symptoms was compatible with ASIA. Most women (75%) with silicone breast implants and unexplained systemic symptoms had pre-existent allergies, suggesting that intolerance to silicone or other substances in the implants might cause these symptoms. In these susceptible women, explantation of the implants may reduce the symptoms. Although the prevalence of this pattern appears to be low, it is of significant importance to recognise these symptoms and consider explantation of the silicone implants and capsulectomy. Therefore, this article's primary message is to recognise and treat this pattern in susceptible women with silicone breast implants. Especially, when the alternative explanations are unavailable, the probable association between the silicone implants and their complaints should be taken seriously.

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Streptozotocin-induced diabetic ketoacidosis in a patient with metastatic islet-cell carcinoma

M. Berends[1], W.J. Lesterhuis[2], H.W.M. van Laarhoven[2,3,*]

[1]Department of Internal Medicine, Maasziekenhuis Pantein, Boxmeer, the Netherlands, [2]Department of Medical Oncology, Academic Medical Center, Amsterdam, the Netherlands, [3]Department of Medical Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands, corresponding author: tel.: +31 (0)20-5665955, fax: +31 (0)20-6919743, e-mail: h.vanlaarhoven@amc.uva.nl

ABSTRACT

Here we report a severe life-threatening complication of treatment with streptozotocin in a patient with pancreatic island-cell carcinoma. The patient was admitted to the intensive care unit with severe diabetic ketoacidosis which needed aggressive fluid resuscitation and insulin therapy. We believe it is critical to be aware of the symptoms of diabetic ketoacidosis and monitor glucose levels during streptozotocin treatment.

KEY WORDS

Clinical oncology, streptozotocin, carcinoma neuroendocrine, diabetic ketoacidosis

INTRODUCTION

Streptozotocin is an antibiotic isolated from *Streptomyces acromogenes*. In oncology streptozotocin is used as a cytotoxic agent to treat islet-cell carcinoma. In functionally active carcinomas streptozotocin is effective in reducing the symptoms of insulin-induced hypoglycaemia.[1] Furthermore, combination with 5-fluorouracil leads to a superior duration of survival compared with streptozotocin monotherapy.[2] Combinations of 5-FU and streptozotocin or doxorubicin and streptozotocin have long been the gold standard chemotherapy regimen for unresectable pancreatic islet-cell tumours.[3] Only recently, promising results for new targeted treatments such as the tyrosine kinase inhibitor sunitinib and the mTOR inhibitor everolimus were reported.[4,5] We describe the case of a 48-year-old woman treated with streptozotocin, who developed a *de novo* diabetic ketoacidosis. To our knowledge this is the first reported case of streptozotocin-induced ketoacidosis in humans.

CASE REPORT

A 48-year-old woman presented to the department of medical oncology with tachypnoa and general weakness. Three years before, she had been diagnosed with metastatic non-secreting low-grade neuroendocrine pancreatic islet-cell carcinoma. She had been treated with streptozotocin and 5-fluorouracil intravenously every six weeks since diagnosis. Computer tomography (CT) scanning one month prior to presentation to the emergency department showed stable disease after 27 cycles of chemotherapy. The last cycle was completed six days before presentation. Physical examination revealed a respiratory rate of 40 breaths/minute, but was otherwise unremarkable. Blood biochemistry showed (normal values between brackets): arterial pH 6.90 (7.36-7.44), pO_2 19.7 kPa (10.0-13.3), pCO_2 0.9 kPa (4.7-6.4), bicarbonate 1.4 mmol/l (22-29) and base excess -29.9 mmol/l (-3-3). The blood glucose level was highly elevated: 28 mmol/l (4.0-5.6). Urinalysis was positive for ketones. Serum antiglutamate decarboxylase (GAD) antibodies were not detectable. We diagnosed *de novo* severe diabetic ketoacidosis. She received intensive fluid resuscitation, intravenous bicarbonate and insulin. Long-acting insulin was started and streptozotocin therapy was discontinued. One year after presentation the patient is still dependent on insulin therapy.

DISCUSSION

The diabetogenic action of streptozotocin was first discovered in 1963.[6] Since then it has been widely used to induce a hyperglycaemic state in animal models studying the pathogenesis of diabetes. It produces a permanent diabetic state in animal models through direct destruction of the pancreatic beta cells. Diabetes

becomes evident after 24 hours of treatment and pancreatic insulin levels fall to 5% of their initial value.[7] It is noteworthy, however, that our patient only developed severe hyperglycaemia after 27 cycles (67.5 g/m^2) of streptozotocin. Indeed, a cumulative toxic effect has been observed in animal models.[8] In an earlier clinical study, however, patients with islet cell tumours received up to 80 g/m^2 of streptozotocin without developing diabetic ketoacidosis.[9] Since the recent CT scan of this patient showed stable disease without gross involvement of the pancreas, we believe that the hyperglycaemic state could not be explained by pancreatic failure due to tumour progression. Therefore, we conclude that the severe diabetic ketoacidosis in this patient was caused by streptozotocin. To the best of our knowledge this is the first reported case of streptozotocin-induced diabetic ketoacidosis in humans. We advise oncologists to monitor glucose levels during streptozotocin treatment.

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REBUTTAL TO LETTER TO THE EDITOR

The challenge of multidisciplinary research: improving diabetic pregnancy together

D.N. Voormolen*, J.H. de Vries, A. Franx, B.W. Mol, I.M. Evers

Department of Obstetrics, University Medical Center Utrecht, Utrecht, the Netherlands,
*corresponding author: d.p.vanmunster-2@umcutrecht.nl

We thank Geelhoed *et al*. for their interest in our paper.[1,2] Our dispute focuses on the type of gluco-monitoring that should be evaluated as well as on the scientific methods used to do that.

With respect to the type of CGM, we evaluate a so-called retrospective or blinded monitoring, while Geelhoed *et al*. advocate real time use. In 2010, when we applied for funding of our study, retrospective monitoring had recently become available, whereas real time monitoring only did so a year after our application. The process of evaluation of health care interventions does not, in our opinion, allow frequent switches of the interventions to be evaluated. We therefore applaud the invitation to evaluate the real time monitor, but we can only start such a project after our current study has been completed. Of note, although Geelhoed *et al*. write 'One does not have to be 'a believer' to hypothesise that this (i.e. real time CGM) may also pertain to pregnant T1D', in fact the only study evaluating real time CGM in diabetic pregnancy did not show any advantages.[3] Also, we encounter many women who drop out of gluco-monitoring in our study, even though we use the retrospective monitoring, that is applied 'only' 25% the time, thus highlighting a potential disadvantage of continuous monitoring. The burden of (RT)-CGM experienced by pregnant women is significant and often a reason to decline, to quit or refuse to use it again in their next pregnancy.[4]

Second, we respectfully disagree with Geelhoed *et al*. on the scientific methods that should be used for evaluation of health care interventions. Although registries such as Geelhoed *et al*. are performing are useful for estimates of prevalence and quality control, they are not suited for the comparative evaluation of health care interventions such as CGM. Thus, unfortunately, their registry will never provide a reliable answer on the question whether CGM is effective over conventional monitoring of diabetes in pregnancy. This is specifically of concern for clinicians who practise in academic centres, as society facilitates these centres in the assumption that they perform sound evaluations of health care.

In view of the fact that our study is halfway – and would probably have been completed if we had joined forces from the start – we propose to collaborate in a next study evaluating RT-CGM.

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