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RESEARCH ARTICLE

Impact of a One Day Crisis Resource Management Training on the Work Satisfaction among Emergency Department Healthcare Staff

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Objective: To evaluate the impact of a single day Crisis Resource Management (CRM) oriented team training, combining didactic and simulation sessions, on work satisfaction of the healthcare staff working in an Emergency Department. **Methods**: Seventy health professionals with different qualifications, working in an emergency department, were enrolled in the study. After enrollment, participants were asked to complete a work satisfaction questionnaire and to choose a day for the training session according to their availability. Each training session took place in the simulation center and consisted of several elements: didactic session and simulation session, followed by instructor facilitated debriefing. The lecture was focused on medical errors and CRM principles. Two months after, they were asked to complete again the work satisfaction questionnaire. **Results**: There were no significant improvements on the items evaluated through the work satisfaction questionnaire for none of the professional categories involved, except for 'the possibility to refer the patient to a specialist whenever was considered necessary' for the doctors. Improvements were seen for the same professional category on the following items: workload, leisure time, level of stress at work, time and energy spent on administrative tasks. **Conclusions**: The findings of this study do not support the effectiveness of a single day CRM training as a tool to improve the work satisfaction among medical staff in ED. Further research is necessary.

Keywords: work satisfaction, crisis resource management, training

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Introduction

Burnout and job dissatisfaction among healthcare staff working in EDs are not rare. Among all specialties, emergency medicine has the highest levels of physician burnout of over 60% [1,2]. Job satisfaction varies between countries, being reported as 65.2% in USA [3], 50-60% in Japan [4], 24.3% in Hong Kong [5]. As job satisfaction acts as a key factor on the individual's and organization's performance and is related to the quality of the provided services [6], efforts to improve it are necessary.

Emergency Department (ED) environments are characterized by difficult working conditions, some of which seem to be common to various clinical settings, independent of the geographical, social and cultural conditions: frequent staff member substitutions, multiple handovers, high workloads and high-risk cases, overcrowding and an increasing access block of the patients are just some of the elements frequently described in literature. Of these factors, ineffective inter-professional communication between healthcare providers seems to lead to fragmentation of the care delivery process, work duplication and problems during handover [7]. All these factors make the ED a place very prone to errors, and an inverse relationship between medical errors and job satisfaction among physicians and nurses has been reported [8,9,10].

As human factors were accounted to be responsible for up to 90% of the accidents in the workplace [11], a training towards improving human factors seems reasonable. With this aim, Crisis Resource Management (CRM) training has been developed by the aviation industry, being responsible for the decreased number of aircraft accidents in the last four decades [12], and then translated into the high-risk areas in medicine, as anesthesia, intensive care and emergency medicine.

CRM primary objectives are to improve team dynamics, to identify and to help changing mental models that create barriers in adopting effective communication, effective task management, healthy leadership behaviors and to increase awareness. [13].

Promising results on errors reduction and performance improvement in ED, through a formal teamwork training, were reported by Morey et al [14].

It would be intuitive to assume that an educational intervention aimed at improving communication, team dynamics and reducing errors would lead to an indirect and at least partial improvement in work satisfaction scores.

However, few data are available regarding the impact of this type of training on the general work satisfaction and even less information specifically linked to the impact of simulation-based educational interventions.

This study is aimed to assess whether a single day CRM oriented team training combining didactic and simulation sessions can improve work satisfaction among the medical staff working in an Emergency Department.

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Methods

Study design

This study is a part of a larger prospective interventional study assessing the impact of a single day CRM oriented training on technical and nontechnical skills of medical staff working in the ED.

Our study was conducted in the Tirgu-Mures Emergency Clinical County Hospital, Romania. The hospital has a five-year emergency medicine residency training program as well as an affiliated simulation center dedicated to multidisciplinary and inter-professional training in emergency and disaster medicine. The annual census of this emergency department is approximately 77,000 patients of whom around 10 % are critical patients.

All medical staff without prior CRM training, excluding first-year emergency medicine residents with less than three months experience in ED, were invited to participate.

Seventy staff members volunteered for this study between March and July 2016: 20 emergency medicine attending physicians, 10 emergency medicine residents, and 40 nurses.

The study protocol was approved by the Ethics Committee of the Tirgu-Mures Emergency Clinical County Hospital and informed consent was obtained from all participants.

After enrollment, participants were asked to complete a work satisfaction questionnaire (Figure 1). The questionnaire was anonymous. We established a period of ten days dedicated to training sessions. The participants were invited to choose a day for the training session according to their availability. The training sessions took place in the simulation center, where we reproduced the ED's resuscitation room conditions. Each training session lasted one day (6 to 7 hours) and consisted of several elements. Initially participants received a lecture focused on medical errors and CRM principles (Figure 2). The role of human factors in errors' occurrence was emphasized as well as the role of CRM training in averting their appearance or mitigating their effects. After the lecture, but before starting the simulation scenarios, participants had the opportunity to familiarize themselves with the manikin and the simulation setting.

For each session, we had two interprofessional teams consisting of one attending physician, one resident and two nurses. We ran six scenarios representing critical patients (four medical cases and two trauma cases). One team ran through a scenario while the other team observed the exercise from a remote room via a high-resolution real time video transmission system. Each team was exposed to all cases, participating actively in three scenarios and being observers for the other three.

The simulation was run by two instructors with CRM background training (one doctor and one nurse) and an IT technician. Each scenario was followed by an instructor facilitated debriefing. Both technical and non-technical issues relating to team performance and team work were discussed, all clinical errors were addressed either by the participants or by the instructors. Both teams were involved in each debriefing, but the active participants had priority in providing feedback. All the participants were encouraged to speak up regardless of their profession (doctor or nurse) and experience.

Two months after this training session, the participants were asked to complete again the work satisfaction questionnaire.

The questionnaire used in this study was designed to measure the work satisfaction among physicians and was validated by Bovier P and Perneger T, being published in 2003. [15].

The questionnaire was translated from French to Romanian by one of the authors of this study (TS) and from Romanian to French by a native French speaker (DF).

The questionnaire has five domains of satisfaction with one to four items: patient care, work-related burden, income-prestige, personal-rewards and relations with colleagues (Figure 1 and 2).

The item "the way you are currently paid (fee-for-service, salary, capitation, etc.) was removed from the original questionnaire as it was not applicable in our situation (all the participants being employees and receiving a salary).

The item "Your professional relations and interactions with other medical doctors" was divided in two: relations with doctors from the ED and with doctors from other

Please indicate how satisfied you are with the following aspects of your professional life:

Patient care
- Your relations with your patients…….
- The possibility to treat your patients as you see it…….
- The possibility to refer your patients to a specialist whenever you think it is necessary…….
- The quality of care you are able to provide…….

Burden
- Your workload……..
- The time you have for family, friends or leisure activities……..
- The level of stress you experience at work…….
- The time and energy you spend on administrative tasks……

Income-prestige
- Your current income…….
- Your social status and the respect people show you……

Personal rewards
- Your intellectual stimulation at work……
- Your opportunities for continuing medical education…….
- Your enjoyment at work……..

Professional relations
- Your professional relations and interactions with other medical doctors from your department…….
- Your professional relations and interactions with other medical doctors from other specialties……..
- Your relations with non-medical staff (nurse, assistant)……

General item
- All things considered, your professional situation at this time……

Fig. 1. Work satisfaction questionnaire

Know your environment (location and function of equipment, human resources and the level of experience, cultural environment)
Anticipate, share and review the plan
Ensure leadership and role clarity
Communicate effectively
Call for help early
Allocate attention wisely- avoid fixation
Distribute the workload- monitor and support team members

Fig. 2. CRM key principles according based on the work of Gaba and Salas, modified by Carne [15]

specialties, as interaction with others specialist doctors who don't understand the functioning of the ED might be a reason of dissatisfaction for the medical staff working in ED.

Participants were asked to rate their satisfaction degree for each item, using a 7-points Likert scale, 1 being extremely dissatisfied and 7 being extremely satisfied.

Statistical analysis

All data were collected in a Microsoft Excel Spreadsheet, independently for doctors and nurses. Graph Pad Prisma 5 and Microsoft Excel programs were used to analyze the data. The normality test used was D'Agostino.

This analysis revealed that the data series were non-gaussian, with skewed distribution curves. Next statistical analysis tests were performed considering the fact that our data were non-gaussian, therefore median and interquartile range (IQR) were used to describe each data series, and Wilcoxon signed-rank test to assess the statistical significance for central tendency difference. The significance level used in all statistical tests was 0.05.

Results

Seventy participants were enrolled in the study (30 doctors: 20 attending physicians and 10 residents, representing 94% of the total numbers of doctors without previous CRM training and 40 nurses, representing 69% of the total number of nurses without previous CRM training). Sixty-three completed the study. Seven participants (2 doctors and 5 nurses) didn't complete the questionnaire two month after the training, but they attended the training. Out of the 5 nurses, one resigned her position and was not available for the final assessment.

The male: female ratio was 13:17 for doctors and 11:29 for nurses. Professional experience was variable (average 70 months, minimum 8 and maximum 300 months).

The mean experience of work in the emergency department was: 149 months (minimum 72 and maximum 300 months) for the EM attendings, 30 months (minimum 12, maximum 52 months) for the residents and 38 months (minimum 8 and maximum 156 months) for nurses.

Collected data were analyzed separately for doctors and nurses. Results are reported in Table I and Table II.

In general, doctors were satisfied with the current work situation, for most of the items evaluated median being 5 or 6, before and after training. The worst aspects according to their rating were the workload (median 2), the leisure time (median 3), the level of stress at work (median 3), the time and the energy spent on administrative tasks (median 3). An improvement was seen after the training for the level of stress at work (median 4.5) and time spent on administrative work (median 4), but significance level was not reached. A significant change in a positive way was noticed on the possibility to refer the patients to a specialist if necessary (p=0,025).

According to their rating, nurses were also satisfied with their work situation, for most of the elements median being 5 or 6 and the training didn't change significantly their perception. The lowest score was given for the workload (median 4) and the highest one (7) was given for the opportunities for continuing medical education.

Discussions

Work satisfaction is a complex variable and one of the most researched within the field of occupational and organizational psychology. It has been defined as 'a measure of workers' contentedness with their job, whether or not they like the job or individual aspects or facets of jobs, such as nature of work or supervision.' [17] People's attitudes towards their work life influence the quantity and quality of work that individuals will develop as well as other variables

Table I. Results of the work satisfaction questionnaire for physician

	Element	Initial assessment		Final assessment		P value*
		Median	IQR	Median	IQR	
Patient care	Your relations with your patients	5	2	5	1	0.739
	The possibility to treat your patients as you see it	5.5	2	6	1.75	0.390
	The possibility to refer your patients to a specialist whenever you think is necessary	4	2.25	5	3	0.025
	The quality of care you are able to provide	6	1	6	0.75	0.928
Burden	Your workload	2	3	2	3.75	0.290
	The time you have for family, friends or leisure activities	3	1	3	2	0.322
	The level of stress you experience at work	3	3	4.5	3	0.435
	The time and energy you spend on administrative tasks	3	2.25	4	2	0.448
Income-prestige	Your current income	4.5	2.25	5	2	0.253
	Your social status and the respect people show you	5	2.25	5	3	0.907
Personal rewards	Your intellectual stimulation at work	5.5	1.25	5	2	0.524
	Your opportunities for continuing medical education	6	2	6	2	0.598
	Your enjoyment at work	5	2.25	5	1.75	0.242
Professional relations	Your professional relations and interactions with medical doctors from your department	6	0.25	6	1	0.146
	Your professional relations and interactions with medical doctors from other specialties	5	1.25	5	1.75	0.884
	Your relations with non-medical staff (nurse, assistant)	6	1.25	6	2	0.213
General item	All things considered, your professional situation at this time	5	1.25	5	1	0.306

*Wilcoxon test

Table II. Results of the work satisfaction questionnaire for nurses

		Initial assessment		Final assessment		P value*
	Element	Median	IQR	Median	IQR	
Patient care	Your relations with your patients	6	1	5	1	0.305
	The possibility to treat your patients as you see it	6	2	6	2	0.674
	The possibility to refer your patients to a specialist whenever you think is necessary	5	2.5	5	2	0.477
	The quality of care you are able to provide	6	2	6	1	0.183
Burden	Your workload	4	3	4	3	0.540
	The time you have for family, friends or leisure activities	5	3	4	2	0.642
	The level of stress you experience at work	5	2	4	3	0.398
	The time and energy you spend on administrative tasks	5	2	5	1	0.340
Income-prestige	Your current income	5	2	4	3	0.103
	Your social status and the respect people show you	6	1	6	1	0.521
Personal rewards	Your intellectual stimulation at work	6	1.5	6	1	0.955
	Your opportunities for continuing medical education	7	1	7	1	0.802
	Your enjoyment at work	6	1	6	2	0.450
Professional relations	Your professional relations and interactions with medical doctors from your department	6	2	6	1	0.713
	Your professional relations and interactions with medical doctors from other specialties	6	1.5	5	2	0.677
	Your relations with non-medical staff (nurse, assistant)	6	1	6	1	0.571
General item	All things considered, your professional situation at this time	5	1	6	1	0.308

*Wilcoxon test

such as absenteeism, tendency to leave the organization, and high rotation rates [18].It seems to be impacted by an increasing number of factors, both intrinsic and extrinsic, such as conflict, compensation and pay, workload, interpersonal relationships, career development, information access and feedback [19].

Very few data connecting CRM training and job satisfaction are available in the literature. To our knowledge, this is the first study that assesses the effects of a CRM oriented training performed in a safe and friendly environment (the simulation center) on the perception of overall work satisfaction among Emergency Department medical staff in Romania.

Work satisfaction was measured through a questionnaire that has five specific domains and a general one.

Patient Care

This topic refers mostly to the complex interactions between physician, patient and the healthcare system. CRM training provided during this study covered only a very small portion of this topic, as it was intended to improve team dynamics in emergency and time pressured situations. ED team members were trained to adopt behaviors that would prevent human errors and thus ensure higher levels of patient safety during acute care, such as being aware of the possible dangers and communicating them assertively regarding their hierarchical status, exercising leadership and fellowship, mobilizing all the available resources, preventing and managing fixation errors, distributing the workload etc. The only significant change (p=0.025) seen after the training, and only for the physicians, regards the possibility to refer the patient to a specialist when considered necessary. This result is difficult to interpret in the context of CRM training. We are not sure whether their answer is reflecting one of the principles taught during the training, namely "calling for help early", as this should be applied to difficult situations when quick help is necessary or is referring to the possibility to admit or to send the patient to another specialist doctor. If the second possibility is the real one, the lack of change for the same item in the case of nurses is not surprising, as disposition is not their responsibility. Even more, some studies found that dissatisfied physicians used more total outpatient procedures and made more referrals than physicians who are satisfied. [5,20] As shown by Boet et al. in a systematic review, there are few studies that followed and demonstrated the transfer of CRM skills learned to clinical settings and even less on patient's outcome improvement [21]. Little is known about the impact of these skills on healthcare provider-patient interactions and the overall patient care.

Burden

The lowest scores were given by both professional categories, physicians and nurses before and after the training for the workload and 'time to spend with the family, friends or for leisure activities'. These findings are in accordance with the existing literature on the subject, both of them being reasons for work dissatisfaction and for the intention to leave, among physicians and nurses working in EDs [5,22]. Morey et al, showed a significant decrease in error rate and an improvement in staff attitude through a teamwork-oriented training, but no difference was found in the subjective workload experience [14]. The lack of personnel and the elevated healthcare work burden are among the reasons that explain it. Strategies to improve these aspects are necessary. According to Suarez et al, rotation between different acuity levels in the ED seems to play a protective role against job dissatisfaction [22]. However, in the physician's group an improvement was noticed on the 'level of stress at work' and 'time and energy spent on administrative

tasks'. These might have been influenced by CRM training. Complex, rapidly evolving or unfamiliar emergency cases can be extremely stressful events for members of the ED. Principles such as: know your environment, anticipate, share, communicate effectively, call for help, distribute the workload are emphasized during the CRM training and could have played a role. Kaissi et al, demonstrated that effective teamwork can lead to increased control over the work environment in hospital high-risk areas: emergency department, intensive care unit, operating theatre. This control was reflected in an increase of effectiveness, time efficiency, staff morale and patient satisfaction, as well as lower stress for staff and patients [23].

Income-Prestige

Concerning salary and prestige, there were no statistically significant differences, which is not surprising, as these elements couldn't be directly influenced by the training.

Personal rewards

No statistically significant changes were noted in this domain, although findings across literature suggest that simulation-based training may serve as an enjoyable, applicable, and realistic tool to enhance a team's performance across all caregivers and different levels of experience. [24]. According to their scores, our participants were quite satisfied with these aspects even before training, particularly with 'opportunities for continuing medical education' (median 6 for doctors and 7 for nurses). This might be explained by the easy access of the staff working in this specific ED, to different courses that are organized in the simulation center.

Professional relations

The importance of interpersonal relationships at work as a protective factor against stress and professional burnout has been reported previously [21,25].

Although CRM training emphasized the importance of: communication management, reducing the interference of personal problems, reducing the power discrepancy between those in authority and subordinates, debriefing after a case and team building, which could have led to an increase in interactions with peers, no statistically significant changes were noted in our study in professional relations neither inside or outside the department. However, the initial scores were rated quite high (medians of 6 and 5). So, these results were partially expected. Out of 136 ED medical staff members, 110 were exposed to CRM training during the study period or before, with 19% of the clinical staff remaining untrained with regards to teamwork principles. This could lead to a restrain in implementing the acquired knowledge in the work environment, while favoring the 'traditional' way of working and communicating. There is also a high rate of staff renewing, which requires time to integrate new members into a team and to operate at high standards. Also, the duration of the CRM training might be insufficient to change attitudes and behaviors that have been formed and consolidated over the years. Increasing the length of the training or periodically repeating the simulation session might increase its effect.

General score of satisfaction

The general level of satisfaction did not seem to be influenced by the training in the case of physicians and only slightly improved in the case of nurses. This is in accordance with a similar study conducted by Meurling et all in 2013 in Sweden, on 151 ICU staff members (physicians, nurses and nurse assistants). Comparable to our study, the ICU staff was exposed to 1 day of training including 5 standardized scenarios, with structured debriefing aimed at clinical performance and CRM based behavior targets. Job satisfaction was a secondary objective of their study. The results showed an improvement of self-efficacy scores for nurses and physicians as well as of the perceived quality of collaboration and communication with other physicians after the training. Teamwork, safety climate and working conditions were perceived more positive at the end of the study, by nurse assistants. The number of nurses quitting their job and the time of sick leave for nurses decreased from 28% to 12% during the study period (2006-2010) [26]. Interestingly, however was that job satisfaction scores did not change and even showed a slight decrease for the nurse category.

Limitations

This study has several limitations. Despite the high percentage of participation, not all the professionals in the ED were included. This fact may have influenced some of the results. For the purpose of our study we used a validated job satisfaction questionnaire which was developed based on the main components of work satisfaction identified by qualitative research of the Society of General Internal Medicine Career Satisfaction Study Group. This tool was validated on a group of 1184 physicians, members of the Geneva Medical Association. They have different specialties and most of them were working in the private sector and were paid on a fee-for-service basis [15]. The context and the target group for which this tool was validated are different that those in our study. Medical practice in the ED has unique characteristics in the healthcare system which make it more prone to notable physical and mental distress of the healthcare workers, to burnout and to work dissatisfaction [27]. In our hospital the work is delivered in a state sector and involves frequent overcrowding, scarcity of resources, a generally stressful and sometimes even hostile setting. However, to our knowledge nowadays there is no concise and pragmatic instrument that follows a framework for validity specifically designed for measuring work satisfaction among ED's staff. The correlation with preexisting literature was limited by scarce studies sharing the same interest. Another weakness might be the lack of an evaluation immediately after the training, due to limited

resources. We don't know if during these two months the effect of the training faded or improved.

Conclusions

While reports in literature show that simulation-based training which includes CRM principles can improve elements associated directly or indirectly with work satisfaction (teamwork, communication, sickness absenteeism), the findings of our study are not supporting the effectiveness of CRM training on work satisfaction among ED medical staff.

Further studies are needed to confirm whether familiarizing emergency medical staff with the concepts of efficient teamwork in difficult situations, all under the safety conditions provided by a simulation center, could influence some aspects of work satisfaction, such as the quality of care provided to patients, intra and inter-professional relationships, stress management at work and intellectual stimulation.

Developing a specific questionnaire dedicated and validated for the study target group, including the whole ED's staff and expanding the duration of the training would be necessary.

Authors' contribution

TST – Conceptualization, investigation, methodology, writing original draft

IB – Investigation, writing – original draft

CB – Methodology, supervision, validation, writing review and editing

MP – Formal analysis, validation, writing review and editing

DAM – Investigation, validation, writing review and editing

SMC – Data curation, supervision, validation, writing review and editing

Conflict of interest

Non to declare.

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RESEARCH ARTICLE

Predictors of Progression of Coronary Atherosclerosis after Percutaneous Coronary Intervention

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Objective: This study investigated predictors of progression of coronary atherosclerosis after percutaneous coronary intervention. Their identification may be useful in clinical practice. **Methods**: We retrospectively reviewed the database of the Cardiology Department of the Cardiovascular Disease and Heart Transplant Institute in Tirgu Mures from January 2012 to December 2015 and identified 180 patients readmitted after successful percutaneous coronary intervention. The t-test, chi-square test, Fisher's exact test, and mono- and multivariate analyses were used to evaluate associations between the patients' clinical and angiographic characteristics and the progression of coronary atherosclerosis. **Results**: The pre-percutaneous coronary intervention atherosclerotic burden was associated with a higher number of new coronary lesions at readmission. Hypertension and the placement of more than one bare-metal stent in the right coronary artery were associated with increased odds of the progression of coronary atherosclerosis. The use of drug-eluting stents at the index percutaneous coronary intervention and a greater number of drug-eluting stents in the left anterior descending artery were associated with a decreased chance of the progression of coronary atherosclerosis. **Conclusions**: A massive atherosclerotic load at index percutaneous coronary intervention and hypertension were predictors of the progression of coronary artery atherosclerosis. The number, type, and localisation of the stent at the index percutaneous intervention could influence the progression of coronary atherosclerosis. Further research is needed to identify other potential predictors and to determine how to optimize the treatment of known predictors.

Keywords: progression of coronary atherosclerosis, percutaneous coronary intervention, drug-eluting stents, bare-metal stent

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Introduction

The impressive progress in coronary stents has been accompanied by a considerable decrease in the need for revascularisation related to the target vessel treated at baseline [1]. Preventing the progression of coronary atherosclerosis by involving new vascular territories after successful percutaneous coronary intervention (PCI) is considered an attractive target. The present study aimed to assess the factors associated with the progression of coronary atherosclerosis after PCI. Their identification and treatment could influence the post-PCI prognosis of patients.

Methods

In order to identify predictors of the progression of coronary atherosclerosis, we reviewed the files of patients hospitalised in the Cardiology Department of the Cardiovascular Disease and Heart Transplant Institute in Tirgu Mures after successful PCI from January 2012 to December 2015. Only patients with coronary angiography upon readmission were included in the study.

The progression of coronary atherosclerosis was defined as follows:

- a reduction of ≥ 10% in the diameter of a pre-existing stenosis ≥ 50%
- 30% reduction in the diameter of a pre-existing stenosis < 50%
- the progression of stenosis to occlusion

The risk factors for cardiovascular disease, comorbidities, details related to the stent used at index PCI (type, number, localisation), and medication after the index PCI were used to compare patients in the group who experienced the progression of coronary atherosclerosis (group B) to those in whom it did not occur (group A).

The data were analysed using the STATA program (version 14.0, Stata Corporation, College Station, TX, USA). Continuous variables were expressed as mean ± standard deviation and were compared using the statistical significance t-tests and linear regression. The categorical variables were expressed as frequency and proportions. Comparisons were made using contingency tables, the chi-square test, and Fisher's exact test. In order to determine the meaning, significance, and strength of the relationships between the variables, logistic regression was used, with the result of

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the mono- and multivariate analyses being described as an odds ratio (OR) associated with a confidence interval of 95%. A p value of 0.05 was considered statistically significant.

The study design was approved by the institutional ethics review board, and all patients provided informed consent.

Results

In 137 patients (76.11%), at least one of the conditions for the progression of coronary atherosclerosis was met, while lesion regression was not found in any patients. Forty-three patients (23.88%) showed stable coronary lesions.

The massive atherosclerotic load found on the index PCI was associated with a higher number of new post-PCI lesions at readmission (p = 0.0002, rho = 0.278), suggesting the progression of coronary lesions (Table I).

The mean duration of follow-up was 29 ± 32 months for group A and 31 ± 32 months for group B (OR 1.001, p = 0.958). The progression of coronary atherosclerosis occurred in the coronary stents in 32 patients (23.35%), in the native coronary arteries in 64 patients (46.71%), and both in the stents and in the native coronary arteries in 41 patients (29.92%).

The demographic and clinical characteristics of the patients are shown in Table II.

A lack of anginal symptoms was a good predictor for group A (OR 0.36, p = 0.018), while acute coronary syn-

Table I. Results of the pre-PCI and readmission coronarography

Parameter		Pre-PCI coronarography	Readmission coronarography
Number of coronary lesions	Monovascular	78 (43.33)	72 (40)
	Bivascular	63 (35)	27 (15)
	Trivascular	34 (18.89)	10 (5.56)
	> 3	5 (2.78)	0
	Without lesions	0	71 (39.44)
Coronary lesion localisation	Left main coronary artery	6 (1.8)	4 (2.22)
	LAD	128 (39.38)	43 (23.88)
	RCA	85 (26.15)	46 (25.55)
	Left circumflex coronary artery	60 (18.46)	18 (10)
	Other coronary artery	43 (14.15)	43 (23.88)

Data are expressed as number (%).
LAD: Left anterior descending artery; PCI: percutaneous coronary intervention; RCA: right coronary artery

Table II. Demographic and clinical characteristics: group A vs group B

Parameter		Group A 43 (23.88)	Group B 137 (76.11)	p
Age, years		61.17 ± 8.34	62.25 ± 10.38	0.595*
Male sex		32 (74.41)	99 (72.26)	0.745**
Cardiovascular risk factors	Hypertension	34 (79.06)	126 (91.19)	0.004**
	Diabetes mellitus	7 (16.27)	30 (21.89)	0.428**
	Obesity	15 (34.83)	35 (25.54)	0.225**
	Smoking	4 (9.3)	19 (13.86)	0.738**
	Hypercholesterolaemia	20 (46.51)	64 (46.71)	0.993**
Comorbidities	Prior myocardial infarction	18 (41.86)	72 (52.55)	0.216**
	Prior aortocoronary bypass	2 (4.65)	7 (5.1)	1**
	eGFR ≤ 60 ml/min/1.73 m^2	8 (18.6)	35 (25.54)	0.352**
	Ejection fraction < 50%	8 (18.6)	32 (23.35)	0.516**
Type of readmission	Chronic	37 (86.36)	86 (67.15)	0.016**
	Emergency	6 (9.3)	45 (32.8)	
Diagnostic at readmission	Stable angina	26 (60.46)	72 (52.55)	0.34**
	Unstable angina	3 (6.97)	33 (24.08)	0.015***
	Acute myocardial infarction	0	9 (6.56)	0.117***
	Cardiological reassessment	12 (27.9)	17 (12.4)	0.015***
Number of stents/patient		1.62 ± 0.92	1.54 ± 0.96	0.313***
Type of stent	DES	18 (41.86)	35 (25.54)	0.038**
	BMS	28 (65.11)	107 (78.1)	0.069**
DES localisation at index PCI	Left main coronary artery	1 (2.32)	3 (2.18)	1***
	LAD	11 (25.58)	22 (16.05)	0.154***
	RCA	6 (13.95)	11 (8.02)	0.243***
	Left circumflex coronary artery	3 (6.97)	6 (4.37)	0.446***
	Other coronary artery	3 (6.97)	5 (3.64)	0.398***
BMS localisation at index PCI	Left main coronary artery	1 (2.32)	1 (0.72)	0.421***
	LAD	19 (44.18)	56 (40.87)	0.686***
	RCA	4 (9.3)	40 (29.19)	0.007***
	Left circumflex coronary artery	8 (18.6)	22 (16.05)	0.689**
	Other coronary artery	4 (9.3)	18 (13.13)	0.602**
Medical therapy	Aspirin	16 (37.2)	57 (41.6)	0.612**
	Dual platelet anti-aggregation	24 (55.81)	68 (49.6)	0.458**
	Angiotensin-converting enzyme inhibitor	21 (48.83)	90 (66.35)	0.041**
	Statin	34 (79.06)	94 (68.61)	0.153**

Data are expressed as number (%) or mean ± standard deviation.
*t-test; **Fisher exact test; ***chi-square test
BMS: bare-metal stents; DES: drug-eluting stents LAD: Left anterior descending artery; PCI: percutaneous coronary intervention; RCA: right coronary artery

drome statistically correlated with group B (OR 5.98, p = 0.004). Stable angina symptomatology did not indicate a significant association with either of the groups (OR 0.7, p = 0.341).

The use of drug-eluting stents at the index PCI and a greater number of drug-eluting stents at the left anterior descending artery (LAD) level decreased the chances for the patient to have progression of coronary atherosclerosis (OR 0.466, p = 0.04, and OR 0.52, p = 0.05) (Table III).

The use of bare-metal stents at the index PCI doubled the chances of the patient being in group B (OR 2), but the statistical significance was poor (p = 0.072). Instead, the placement of more than one bare-metal stent in the right coronary artery almost tripled the chances of being in group B (OR 2.81, p = 0.022) (Table III).

The progression of coronary atherosclerosis in the native coronary artery occurred most frequently in the LAD and the right coronary artery (OR 20.66, p = 0.004 and OR 10.52, p = 0.002) (Figure 1). Of the cardiovascular risk factors, only hypertension was statistically associated with the progression of atherosclerotic lesions (p = 0.004). We found a statistically significant association between the use of angiotensin-converting-enzyme inhibitors (ACEI) and the progression of coronary atherosclerosis (p = 0.041).

Discussion

In our study population, the predictors for the progression of coronary atherosclerosis after successful PCI were a greater pre-PCI atherosclerotic burden, in particular hypertension, and the placement of more than one bare-metal stent in the right coronary artery. The use of drug-eluting stents and a greater number of drug-eluting stents in the LAD were associated with a lack of progression of coronary atherosclerosis. In the native coronary artery, progression of atherosclerosis occurred more frequently in the LAD and in the right coronary artery territory.

Pre-PCI multi-vascular coronary lesions are commonly associated with the development of new post-PCI coronary lesions [2,3]. In agreement with previous research, a positive correlation was found in our study between the massive atherosclerotic load found on pre-PCI coronarography and multi-vascular coronary heart disease upon re-admission, suggesting the progression of existing coronary lesions or the occurrence of new lesions. The progression of coronary atherosclerosis was found in two-thirds of our patients, but regression was not found in any patients.

Hypertension is a well-known atherogenic risk factor [4]. In our study, hypertension was the only cardiovascular risk factor associated with progression of coronary

Table III. Correlation between the progression of coronary atherosclerosis and the stents type, their number, and localisation in coronary artery

Stent type	Localisation at index PCI	Stents number			p	OR	SE	95% CI
		1	2	3				
DES	Left main coronary artery	4 (9.3)	0	0	0.956	0.94	1.095	0.0948567-9.265621
	LAD	27 (62.79)	6 (13.95)	0	0.045	0.52	0.16	0.2737484-0.9865113
	RCA	16 (37.2)	1 (2.3)	0	0.352	0.626	0.21	0.2338576-1.676849
	Left circumflex coronary artery	8 (18.6)	1 (2.3)	0	0.277	0.515	0.315	0.1553879-1.706088
	Other coronary artery	7 (16.27)	1 (2.3)	0	0.542	0.67	0.44	0.1864483-2.415322
BMS	Left main coronary artery	2 (1.45)	0	0	0.408	0.3	0.44	0.0188164-5.031484
	LAD	64 (46.71)	10 (7.29)	1 (0.72)	0.524	0.84	0.23	0.4886101-1.439753
	RCA	32 (23.35)	9 (6.56)	3 (2.15)	0.022	2.81	1.26	1.164559-6.802204
	Left circumflex coronary artery	29 (21.16)	1 (0.72)	0	0.784	0.89	0.388	0.3758553-2.093628
	Other coronary artery	21 (15.32)	1 (0.72)	0	0.461	1.51	0.85	0.5033165-4.55136

Data are expressed as number (%)
BMS: bare-metal stents; DES: drug-eluting stent; LAD: left anterior descending artery; OR: odds ration; PCI: percutaneous coronary intervention; RCA: right coronary artery; SE: standard error; CI: confidence interval

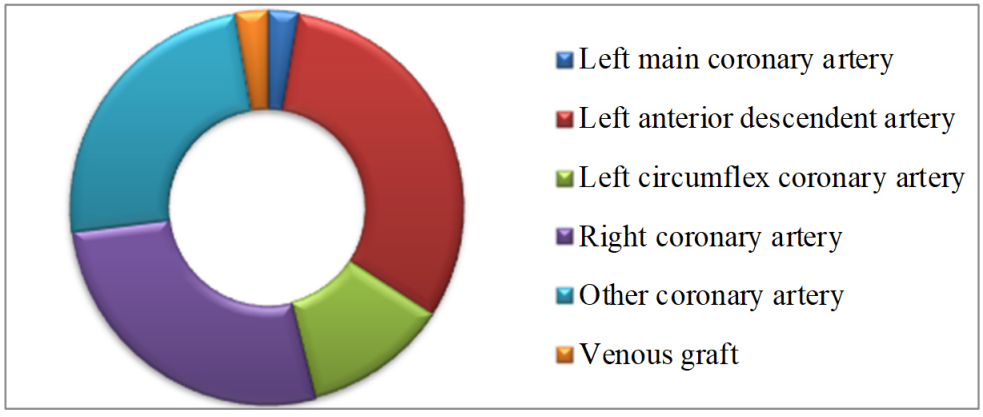

Fig. 1. Progression of atherosclerosis in the native coronary artery by location

atherosclerosis. Similar to our study, Borges et al. found that hypertension, along with male sex, is a predictive factor for the progression of coronary atherosclerosis [5]. The importance of aggressive treatment of all risk factors for cardiovascular disease is highlighted in the COURAGE trial, where patients with optimal medical therapy (intensive pharmacologic therapy and lifestyle intervention) had fewer cardiovascular events than PCI-treated patients [6].

The superiority of using drug-eluting stents compared to bare-metal stents in order to reduce the need for revascularisation related to the initially treated target vessel has been demonstrated in several trials [7,8]. However, in a study involving 428 patients randomised to PCI with drug-eluting stents or bare-metal stents, Zelwegger et al. concluded that the progression of coronary atherosclerosis was similar between the two groups regardless of the type of stent used in the index PCI [9]. In our study, the use of drug-eluting stents at the index PCI was a predictor for the absence of the progression of coronary atherosclerosis.

The progression of coronary atherosclerosis in the native coronary arteries has shown conflicting data. In the CASS trial, in patients treated with CABG, the progression of coronary atherosclerosis was more aggressive in LAD territory [10]. Additionally, Borges et al. found that PCI-treated patients had more progression of coronary atherosclerosis in LAD territory [5]. On the contrary, in the INTACT trial, the progression of coronary atherosclerosis occurred more frequently in the right coronary artery territory [11]. In our study, first the LAD and then the right coronary artery territory was associated with the progression of coronary atherosclerosis. Interestingly, in our study, a greater number of drug-eluting stents in the LAD was associated with a lack of progression of coronary atherosclerosis, while the placement of more than one bare-metal stent in the right coronary artery was a predictor for the progression of coronary atherosclerosis. We did not find any data in the literature about the association between placement, the number of drug-eluting stents/bare-metal stents at index PCI, and the progression of coronary atherosclerosis.

Numerous studies have demonstrated the beneficial effects of ACEI in patients with ischemic coronary artery disease, not only in reducing blood pressure but also in stabilising the atheromatous plaque and inducing the regression of uncalcified coronary stenoses [12,13]. In contrast, our study found a statistically significant association between the presence of ACEI and the progression of coronary atherosclerosis. This can be explained from at least from two points of view. First, hypertension, whose first line of treatment is ACEI, was statistically associated with the same group. Secondly, the study did not investigate the type and intensity of treatment with ACEI, and the effect of ACEI is not equal for all components of the class.

Our study has a few limitations. The present study was a single centre, retrospective study, and thus, our conclusions are not generalisable. Second, the small sample size reduced the statistical power to detect association with other predictive factors for the progression of coronary atherosclerosis.

Conclusion

A massive pre-PCI atherosclerotic load and hypertension were predictors of the progression of coronary artery atherosclerosis. The number, type, and localisation of the stent at the index percutaneous intervention could influence the progression of coronary atherosclerosis. Further research is needed in order to identify other potential predictors and to determine how to optimize the treatment of known predictors.

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Conflict of interest

None to declare.

Author's contribution

VD - Conceptualization, data curation, formal analysis, investigation, methodology, supervision, validation, visualization, writing original draft, writing review and editing
MD - Conceptualization, data curation, formal analysis, investigation, supervision, writing review and editing
IVS - Conceptualization, formal analysis, methodology, validation, writing review and editing
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RESEARCH ARTICLE

Risk of Contrast-Induced Nephropathy after Repeated Contrast Medium Administration

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Objective: Non-invasive coronary computed tomography angiography is frequently used to exclude coronary artery disease in patients with low-to-intermediate pre-test probability because of the high negative predictive value. The strategy of coronary computed tomography angiography and subsequent invasive coronary angiography in case of positive findings has risks owing to repeated contrast medium administration and the possibility of contrast-induced nephropathy. **Methods**: We retrospectively evaluated the changes in the serum creatinine level and estimated glomerular filtration rate (at baseline, 24 h, and 48 h after contrast administration) in patients with repeated contrast medium administration in order to evaluate contrast-induced nephropathy development. All patients were intravenously hydrated with 1000 ml sodium chloride (0.9%) per day during hospitalization. **Results**: The study included 17 patients. Of these patients, 7 (41.2%) had prior impaired renal function (estimated glomerular filtration rate <60 ml/min/1.73 m2). The mean coronary computed tomography angiography contrast medium (iopromide 769 mg/ml) volume was 114.11 ± 7.75 ml and the mean invasive coronary angiography contrast medium (iohexol 755 mg/ml) volume was 129.7 ± 19.24 ml. The serum creatinine level was significantly higher and the estimated glomerular filtration rate was significantly lower at 48 hours after the second contrast medium administration than at baseline (p = 0.05 and p = 0.03, respectively). None of the patients had contrast-induced nephropathy. **Conclusion**: Repeated contrast medium administration was not associated with contrast-induced nephropathy development at 48 hours after the second contrast medium administration, even in patients with prior impaired renal function.

Keywords: contrast-induced nephropathy, contrast medium administration, renal function

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Introduction

The rapid evolution of cardiovascular imaging during the last few decades has resulted in an increase in the use of intra-venous/intra-arterial iodinated contrast agents. Conventional invasive coronary angiography (ICA) is the gold standard approach for the evaluation of coronary artery disease (CAD), and non-invasive coronary computed tomography angiography (CCTA) is frequently used to exclude CAD in patients with low-to-intermediate pre-test probability. However, the strategy of CCTA and subsequent ICA in the case of positive findings has some risks owing to repeated contrast exposure and the possibility of subsequent contrast-mediated renal injury. Contrast-induced nephropathy (CIN) was first described in the 1950s [1], and it remains one of the leading causes of hospital-acquired acute renal injury [2]. Several studies have mentioned the incidence of CIN after single administration of radiocontrast medium [3,4]. However, in real life, repeated contrast medium administration (CMA) is not infrequent. The present study aimed to assess the change in renal function after two consecutive imaging procedures involving intra-venous and intra-arterial CMA in order to evaluate CIN development. To our knowledge, the risk of CIN development after CCTA followed by ICA has not been investigated previously.

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Methods

We reviewed the records of patients admitted to our institution for CCTA followed by ICA between January and December 2015. All study participants provided informed consent, and the study design was approved by the appropriate ethics review board.

Renal function was evaluated according to changes in the serum creatinine (sCr) level and eGFR 24 hours after each CMA and 48 hours after the last CMA compared with baseline values (before CMA). The diagnostic criterion for CIN was a rise in the sCr level by 25% or more or an absolute increase in the sCr level by 0.5 mg/dl or more compared with the baseline value. The eGFR was calculated using the Cockroft–Gault formula (creatinine clearance [CrCl] = [140–age] × weight / sCr × 72; $CrCl_{female}$ = CrCl × 0.85 [female sex adjustment]). The results are expressed as mean ± standard deviation (SD), and the data were compared using one-way ANOVA for repeated measurements. All statistical analyses were performed using STATA 14.0 (Stata Corporation, College Station, TX, USA). A p-value ≤0.05 was considered significant.

Results

The study included 17 patients. Prior impaired renal function (eGFR <60 ml/min/1.73 m^2) was noted in 41.2% of the patients, and a history of ST-elevation myocardial infarction (STEMI) was noted in 41.2% of the patients.

The demographic and clinical characteristics of the study patients are presented in Table I.

Table I. Demographic and clinical characteristics of the patients

Parameter	Number (%)
Male	16 (94.1)
Age (mean ± SD), years	61.41 ± 9.007
Hypertension	15 (88.2)
Diabetes mellitus	4 (23.5)
Hypercholesterolemia	6 (35.2)
Smoking history	5 (29.4)
Obesity	4 (23.5)
Prior STEMI	7 (41.2)
Prior non-STEMI	2 (11.8)
eGFR < 60 ml/min/1.73 m^2	7 (41.2)

eGFR: estimated glomerular filtration rate; STEMI: ST-elevation myocardial infarction

The time interval between procedures was 24 hours. In patients with a prior eGFR <60 ml/min/1.73 m^2, ICA was performed after an additional 24-hour period. All patients were intravenously hydrated with 1000 ml sodium chloride (0.9%) per day during hospitalisation. Oral fluid intake was not assessed. Iopromide (769 mg/ml) was used for CCTA, and iohexol (755 mg/ml) was used for ICA.

The mean contrast volume received was 114.11 ± 7.75 ml for iopromide and 129.7 ± 19.24 ml for iohexol.

The sCr levels and eGFRs at baseline, 24 hours after the first CMA (CCTA), and 24 and 48 hours after the second CMA (ICA) are shown in Table II.

There were no significant differences in the mean sCr level and mean eGFR between baseline and 24 hours after ICA (sCr: 0.92 ± 0.28 vs. 0.92 ± 0.33 mg/dl, F(2.32) = 1.6, p = 0.21; eGFR: 95.43 ± 26.69 vs. 94.48 ± 23.3 ml/min/1.73 m^2, F(2.32) = 1.22, p = 0.29). The sCr level was significantly higher and the eGFR was significantly lower 48 hours after ICA than at baseline (sCr: 0.95 ± 0.08 vs. 0.92 ± 0.28 mg/dl, F(3.48) = 3.08, p = 0.05; eGFR: 91.82 ± 21.84 vs. 95.43 ± 26.69 ml/min/1.73 m^2, F(3.48) = 4.13, p = 0.03). None of the patients met the diagnostic criterion for CIN.

Discussion

CIN affects up to 50% of patients at high risk [3], and it is a clinical reality with high health and economic burdens [5]. In a previous large meta-analysis, James et al. found that the presence of CIN following coronary angiography was associated with increased patient mortality and major cardiovascular events [6].

The risk of CIN after a second contrast exposure has been investigated in a few studies. Trivedi et al. reported a CIN incidence of 14.3% after repeated CMA, even in patients with preserved renal function [7]. On the other hand, Winther et al. performed a study on the effect of repeated CMA in patients with end-stage kidney disease and found a low risk of post-contrast acute kidney injury and long-term complications [8].

In the present study, we investigated the impact of both intra-venous and intra-arterial CMA on renal function assessed according to the sCr level and eGFR. The important finding of our study was the complete absence of CIN, even in patients with prior impaired renal function. Only 1 patient showed a significant decrease in the eGFR, resulting in a change in the classification of kidney disease from 3a to 3b. However, this patient had other risk factors for kidney disease, such as hypertension and insulin-dependent diabetes mellitus. Interestingly, several patients showed better values of sCr and eGFR at 24 hours after the first CMA, supporting the hypothesis of the correction of pre-renal dysfunction after the initial procedure by intravenous administration of sodium chloride (0.9%). It is known that oral hydration can improve renal function after CMA [9,10]. However, data on the extent of oral fluid intake before and after CMA were not available.

Our findings appear to confirm previous results indicating the lack of kidney injury after CMA [11,12]. Sinert et al. compared contrast-exposed patients with contrast-unexposed patients and did not find significant kidney injury after CMA in patients with previously normal renal function. In fact, the incidence of acute kidney injury was greater among patients without CMA than among those with CMA (8.9% vs. 5.7%) [13]. Additionally, McDonald et al. did not find a greater risk of nephropathy development in contrast-exposed patients than in contrast-unexposed patients, irrespective of baseline renal function [14]. These findings question whether CMA or other pathological conditions actually cause degradation of renal function.

The present study had several limitations. First, this study had a small sample size. Second, this retrospective study had a possible selection bias (oral hydration status and other prophylactic treatments to prevent CIN). Third, the sCr level and eGFR at 72 hours or more after the second CMA were not assessed. Renal function might decline late after CMA. Thus, further studies with a large sample size and long assessment period are needed.

In conclusion, although the sCr level was high and eGFR was low 48 hours after the second CMA, repeated CMA was not associated with CIN development at this point, even in patients with impaired renal function prior to CMA. Intravenous administration of sodium chloride (0.9%) might help improve renal function before and after CMA.

Table II. Evolution of serum creatinine (sCr) level and estimated glomerular filtration rate (eGFR)

Parameter	Baseline	24 hours after CCTA	24 hours after ICA	48 hours after ICA
sCr (mean ± SD), mg/dl	0.92 ± 0.28	0.89 ± 0.25	0.92 ± 0.33	0.95 ± 0.08
eGFR (mean ± SD), ml/min/1.73 m2	95.43 ± 26.69	97.68 ± 23.95	94.48 ± 23.3	91.82 ± 21.84

CCTA: coronary computed tomography angiography; ICA: invasive coronary angiography

Author's contribution

VD - Conceptualization, data curation, formal analysis, methodology, supervision, validation, visualization, writing original draft, writing review and editing
MD - Data curation, investigation, methodology, validation, writing review and editing
CM - Conceptualization, formal analysis, methodology, validation, writing original draft
IVS - Data curation, formal analysis, methodology, supervision, writing review and editing
MB - Conceptualization, formal analysis, methodology;, supervision, validation, writing review and editing

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Conflict of interest

None to declare.

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RESEARCH ARTICLE

LC-MS Method for Determining Amiodarone and Desethylaminodarone in Rat Plasma Used in Endogenous Overdosing Conditions Following Lipolysis

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Objective: The purpose of this study was to develop a LC-MS method to determine amiodarone (AMI) and its major metabolite desethylamiodarone (DEA) from rat plasma released from the adipose tissue of AMI treated rats subjected to a weight gain/weight loss cycle. **Methods**: Separation of the compounds was performed on a Kinetex 2.6 µm C18 100 x 4.6 mm column under isocratic conditions using a mixture of acetonitrile: 0.1% formic acid 65:35 at a flow rate of 0.5 ml/min. Detection of the analyte was performed by electrospray positive ionization, the monitored ions being 135 m/z from 646 for AMI and 135 m/z of 618 for DEA. Analytes were extracted after plasma protein precipitation with methanol. **Results**: The developed method presented specificity and linearity on the concentration range of 25-2500 ng/ml plasma for AMI and 2.5-1250 ng/ml plasma for DEA and the precision and accuracy of the method at all of quality control concentration levels including LLOQ were according to official guidelines for validating analytical methods. **Conclusions**: A sensitive and accurate LC-MS method has been developed with a much lower LLOQ than literature data to detect the plasma concentration differences of the studied analytes that result from forced lipolysis and mobilization from the adipose tissue.

Keywords: amiodarone, desethylamiodarone, rat, lipolysis

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Introduction

Amiodarone (AMI) is a compound with a particular pharmacodynamic and pharmacotoxicological profile among cardiovascular medication. In addition to antiarrhythmic action as a K^+ channel blocker, it also presents noncompetitive antagonistic action on alpha and beta receptors. In clinical practice, AMI is used to control ventricular and supraventricular tachycardia but also for the prevention of recurrences. AMI increases life expectancy in patients post myocardial infarction or suffering from congestive heart failure [1]. From the pharmacokinetic point of view, it has a variable oral absorption, a bioavailability of 22 - 86% and a high volume of distribution. The half-life is 5-20 hours after a single dose, but is up to 58 days after a long-term treatment [2].

Desethylamiodarone (DEA) is the main metabolite of AMI and presents similar therapeutic and toxicological properties to AMI. Even if plasma concentrations of the metabolite are comparable to those of the active substance, in some tissues, there are differences in concentrations. Until the steady state is established, the active substance and the metabolite accumulate in the tissues. Long-term administration of AMI produces excessive accumulation through a mechanism that can not be explained by classical (single compartment model) pharmacokinetics and involves increasing tissue and plasma concentration by maintaining the initial dose. Nowadays, the use of AMI is often associated with a variety of adverse effects, causing patient noncompliance because of the severe toxicity. Multiple organs are affected, including the lungs [3], liver [4], thyroid gland [5], neurological system, skin and gastrointestinal system. Some of these side effects are reversible, but severe cases have also been reported. The fundamental mechanism of AMI toxicity is not fully known, systemic toxic effects are supposed to be related to the accumulation of phospholipids in the target tissues [6].

Despite the multiple adverse effects, because of the low treatment cost, AMI is the antiarrhythmic of choice in ventricular and supraventricular tachycardia, but due to the tendency of cumulation in different organs, in case of intense lipolysis (diet with the aim of reducing body weight or forced in the case of a stroke or post-acute myocardial infarction) massive release from deposits can lead to exacerbation of adverse effects. Under these circumstances, the aim of the present study is to develop a sensitive and precise LC-MS method to determine AMI and DEA from rat plasma, that can quantify the excess of AMI and DEA released from the deposits in the adipose tissue, following lipolysis in obese animals treated with AMI .

Materials and Methods

Chemicals, reagents, solvents

AMI and DEA standards were purchased from Sigma Aldrich and were> 98% pure. Methanol, acetonitrile and formic acid of analytical grade were purchased from Merck KGaA (Darmstadt, Germany). Distilled water was obtained from a Millipore Direct Q system.

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Preparation of standard solutions

The AMI and DEA 1 mg/ml stock solutions were prepared by weighing 10.56 mg AMI hydrochloride (corresponding to 10 mg AMI) on a Metler Toledo AB 54-S balance which was dissolved in 10 ml of methanol, respectively, 5.29 mg of DEA hydrochloride (corresponding to 5 mg of DEA) dissolved in 5 ml of methanol. Standard work solutions, at 8 concentration levels, were prepared by diluting stock solutions with methanol over the concentration range of 25-2500 ng/ml for AMI and 2.5-1250 ng/ml for DEA. Also, 3 quality control samples (QC) of 75, 1250 and 2000 ng/ml for AMI and 37.5, 625 and 1000 ng/ml for DEA were prepared.

Plasma sample processing

Rat plasma samples were collected by cardiac puncture, in EDTA anticoagulant vials. All procedures on experimental animals were performed in agreement with the Ethics Committee for Scientific Research of the University of Medicine and Pharmacy of Tîrgu Mureş. The plasma calibration curve was constructed on the concentration range of 5-500 ng/ml plasma for AMI and 2.5-250 ng/ml plasma for DEA.

For the calibration curve and plasma QC samples, 120 µl rat plasma was spiked with 40 µl AMI solution and 40 µl DEA solution. Plasma proteins were precipitated with 600 µl methanol and the samples were vortex-mixed for 10 seconds. The mixture was centrifuged for 10 minutes at 10000 rpm. 500 µl supernatant was transferred to a chromatography vial and 5 µl were injected into the chromatographic system.

Chromatographic conditions

Separation of the compounds was performed on an Agilent 1100 Series System (Agilent Technologies, USA) consisting of a quaternary pump, solvent degasser, autosampler with controlled temperature, column thermostat and an Agilent 6410 QQQ mass spectrometer detector with ESI source. Separation was performed on a Kinetex 2.6 µm C18 100 x 4.6 mm column. The mobile phase used for the separation consisted from acetonitrile and 0.1% formic acid in 65:35 isocratic mixture, with a flow rate of 0.5 ml/min.

MS conditions:

- ionization type and mode: ESI+;
- nebulizer nitrogen: 40 psi;
- drying gas: nitrogen, flow rate 8 L/min;

source temperature 350^0 C;

- capillary potential: 4000 V;
- monitoring transitions m/z 646 →135 for AMI and 618 → 135 for DEA.

Results and discussions

AMI determination was performed by molecular ion fragmentation $[M+H]^+$ m/z 646 and DEA starting from $[M+H]^+$ m/z 618 to the m/z 135 fragment for both compounds (Figure 1).

Chromatograms of rat plasma samples spiked with AMI and DEA at the lower limit of quantification (LLOQ) are presented in Figure 2 and 3. Compounds of interest are separated at a retention time of 3.94 min AMI and 3.16 min DEA.

HPLC method performances

Specificity studies

The specificity of the method was verified using 6 blanc rat plasma samples.

Linearity studies

3 calibration curves were prepared, with 8 concentration levels, in rat plasma and the medium calibration curves of

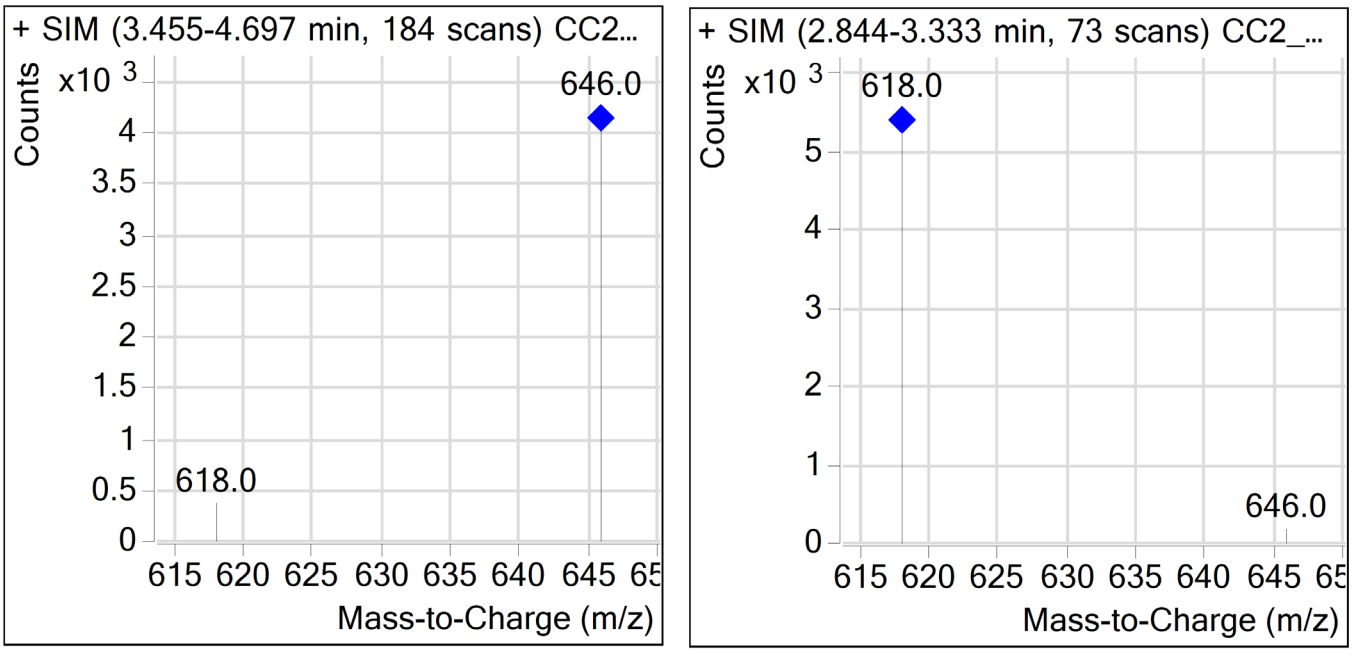

Fig. 1. Full-scan mass spectrum of AMI and DEA in the mobile phase

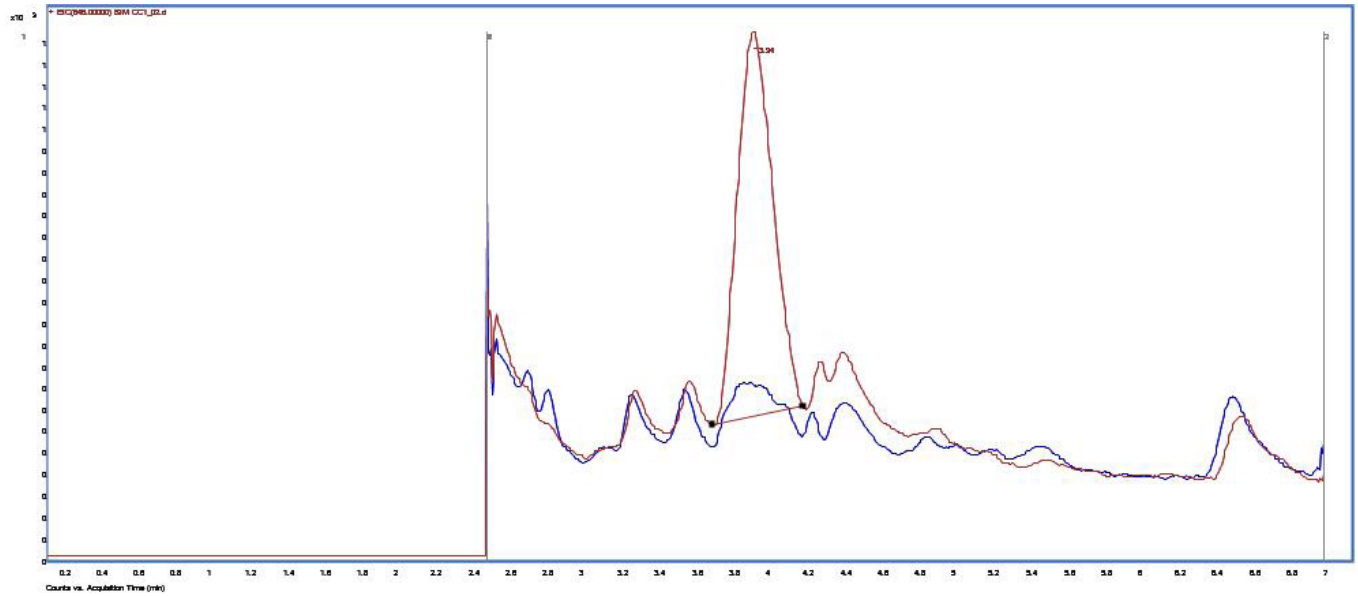

Fig. 2. Chromatogram of a blanc plasma sample (blue line) and an AMI-spiked sample at LLOQ (5 ng/ml plasma)

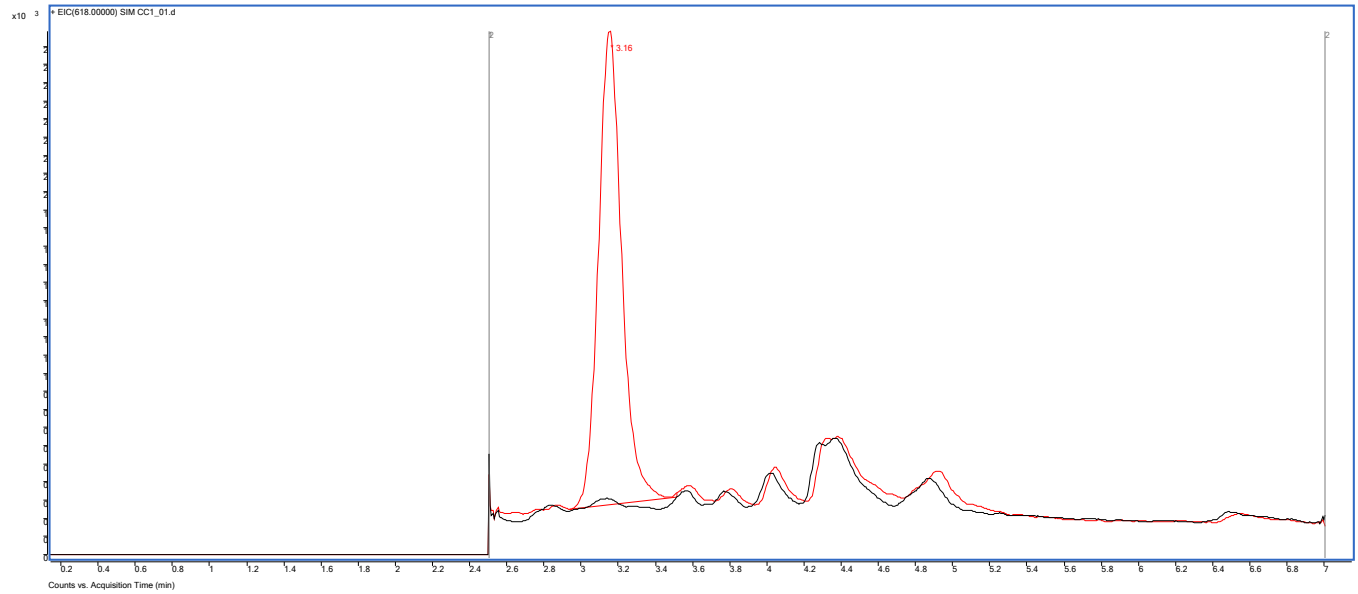

Fig. 3.- Chromatogram of a blank plasma sample (black line) and spiked with DEA at LLOQ (2.5 ng/ml plasma)

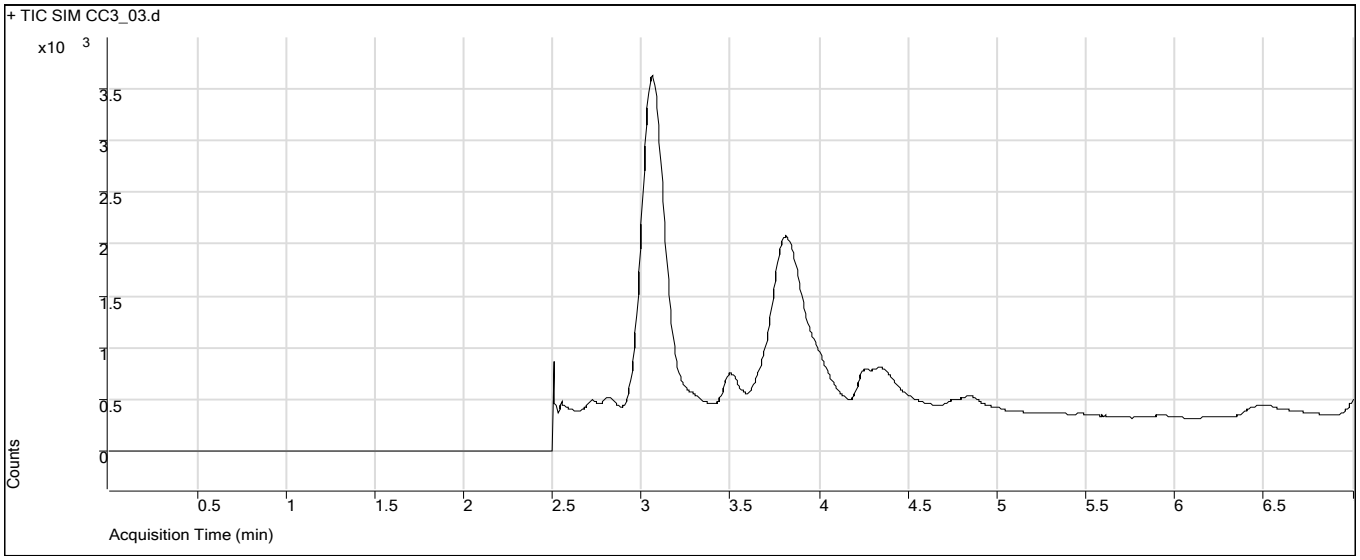

Fig. 4. Chromatogram of a rat plasma sample spiked with AMI and DEA at LLOQ (5 ng/ml plasma AMI and 2.5 ng/ml plasma DEA)

y = a (± SD) x + b (± SD) type, where y-concentration and x-peak area, were y = 1462.40 (±72.95) x + 4679.66 (± 2400.32) for AMI with a determination coefficient R^2> 0,99 and y = 1464.20 (±129.51) x + 15907.33 (±3803.84) for DEA with a determination coefficient R^2> 0.99.

Residuals distribution was random and within ±15% limits. The results demonstrated a good fitting calibration model over the selected concentration range and in accordance to bioanalysis quality criteria.

Precision and accuracy

The precision within- and between-run (CV%) and accuracy (Bias%) were determined during the same series and on different days, on 5 individual LLOQ, QCA, QCB and QCC samples, at concentrations of 5, 15, 250, 400 ng/ml plasma AMI and 2.5, 7.5, 125, 200 ng/ml plasma DEA, according to validation guidelines.

The method presents a good accuracy (101.45% between-run and 98.57% within-run for DEA and 97.68% within-run and 104.76% between-run for AMI) and precision for both compounds (9.4% within-run and 11.12% between-run for AMI and 13.56% within-run and 14.23% between-run for DEA) (Table I and II).

LLOQ was set at 5 ng/ml plasma AMI and 2.5 ng/ml plasma DEA, therefore the LC-MS method developed for AMI and DEA determination in rat plasma presents a much lower LLOQ compared to methods already published in scientific literature [7, 8, 9].

Starting from these premises, the developed method will be used in the study of AMI and DEA plasma levels following chronic treatment in rats undergoing a controlled weight gain/weight loss cycle and compared to a control group (with no significant fluctuations in weight during the experiment). The animal model was chosen according to the similar pharmacokinetic properties of AMI in the two species. Although the microsomal enzyme system differs between human and rat, DEA was confirmed as the active metabolite in both cases [10, 11].

As in the future we aim to determine the plasma concentrations of the two compounds at different time intervals, until complete elimination, an analytical method with increased sensitivity is required.

In addition, in order to demonstrate the applicability of analytical methods, animals received doses of AMI between 25 and 200 mg/kg bw (intraperitoneal or intravenous) *in bolus*; in efficacy and safety studies similar oral doses were administred. However, in the case of oral administration, the plasma concentrations obtained are much lower compared to those obtained after parenteral administration.

Although toxicity mechanisms may vary depending on the organ, numerous studies have shown that the occurrence of side effects is associated with the duration of treatment and excessive accumulation of AMI in the body.

Due to increased lipophilia, AMI is predominantly distributed in adipose tissue with a particular pharmacokinetics in obese patients with frequent cardiac abnormalities, obesity being associated with a pro-inflammatory condition and increased oxidative stress. Administration of AMI to these patients should be made with caution considering the individual variability of pharmacokinetics and the impossibility to monitor plasma concentrations during chronic treatment [12].

In weight-loss diets (obese patients with increased cardiovascular risk at which gradual weight loss is recommended), or in case of forced weight-loss (parenteral nutrition in patients unable to receive a balanced nutritional and caloric intake after myocardial infarction or stroke) by

Table I. Within- and between-run precision, accuracy and recovery for AMI (n = 5)

C nominal ng/ml	Mean C ng/ml (±SD)	Recovery % (±SD)	CV% (Bias%)	Mean C ng/ml (±SD)	Recovery % (±SD)	CV%
		Within-run			Between-run	
5	4.88 (±0.41)	97.68 (±9.24)	9.46 (-2.32)	5.23 (±0.58)	104.76 (±11.65)	11.12 (4.76)
15	15.08 (±0.86)	100.51 (±5.16)	5.74 (0.51)	14.36 (±1.73)	95.76 (±10.34)	12.08 (-3.37)
250	284.52 (±3.73)	113.81 (±1.33)	1.31 (13,81)	283.19 (±8.89)	113.27 (±3.18)	3.14 (13.27)
400	386.54 (±15.88)	96.63 (±3.97)	4.1 (-3,37)	401.80 (±23.00)	100.45 (±5.75)	5.72 (0.45)

Table II. Within- and between-run precision, accuracy and recovery for DEA (n = 5)

C nominal ng/ml	Mean C ng/ml (±SD)	Recovery % (±SD)	CV% (Bias%)	Mean C ng/ml (±SD)	Recovery % (±SD)	CV% (Bias%)
		Within-run			Between-run	
2.5	2.46 (±0.33)	98.57 (±13.37)	13.56 (-1.43)	2.35 (±0,45)	101.45 (±14.52)	14.23 (1.45)
7.5	8.64 (±1.26)	115.33 (±15.08)	14.62 (15.33)	7.64 (±0.51)	101.90 (±6.87)	6.74 (1.90)
125	133.97 (±4.82)	107.17 (±3.45)	3.59 (7.17)	131.29 (±6.19)	105.03 (±4.42)	4.71 (5.03)
200	194.14 (±3.12)	97.07 (±1.56)	1.61 (-2.83)	200.18 (±10.16)	100.09 (±5.08)	5.07 (0,09)

modifying the insulin/glucagon ratio in favor of glucagon, gluconeogenesis from amino acids and lipolysis is induced, the released fatty acids being used to maintain energy cell homeostasis [13]. In this case, AMI and DEA accumulated in the adipose tissue would be mobilized, raising problems both during chronic treatment, by increased plasma levels and toxicity, but also in case of discontinuation of treatment, complete elimination from the body requiers a longer period of time.

Conclusions

The LC-MS method developed to detect AMI and DEA from rat plasma was sensitive and accurate, with an LLOQ (5 ng/ml for AMI, 2.5 ng/ml for DEA), therefore suitable for pharmacokinetic studies, including low doses of substances originated from the adipose tissue deposits and found in plasma after massive lipolysis.

Author's contribution

BEŐ - Conceptualization
GJ - Investigation
SzV - Methodology
AM - Validation
ATV - Writing – original draft

Conflict of interest

None to declare

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RESEARCH ARTICLE

General Characteristics and Quality of Stroke-Related Online Information – A Cross-Sectional Assessment of the Romanian and Hungarian Websites

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Background: The quality of online health-related information may affect users' understanding and medical decision-making with dramatic impact, particularly in case of stroke. **Objective**: The objective of this study was to assess the quality of information about stroke on the Romanian and Hungarian websites in terms of completeness and accuracy. **Methods**: The research was designed as an observational cross-sectional study. The sample included 25 Romanian and 25 Hungarian websites presenting information about stroke for the general public. General characteristics such as website ownership, main goal, website genre and medical approach were identified by the evaluators using a predetermined set of common instructions. The completeness and accuracy of the information were assessed by two independent assessors against a quality benchmark. **Results**: Overall, most of the websites were owned by private commercial companies (42%), had educational goal (66%), were designed as medical web-portals (46%) and had a conventional medicine approach (72%). Mean completeness score was 5.6 points (SD± 1.9) for Romanian sites and 4.1 points (SD ± 2.4) for Hungarian sites (p = 0.017). Mean accuracy score was 6.2 points (SD ± 1.1) for Romanian sites and 7.0 points (SD ± 0.7) for Hungarian sites (p = 0.02). **Conclusions**: The information about stroke on the Romanian and Hungarian websites had poor quality. Although we found statistically significant differences between the quality scores of the two language sub-samples and two site characteristics associated with significantly higher quality, the practical relevance of these findings for online health information seekers should be interpreted with caution.

Keywords: e-health, consumer-health, health-related information, stroke, Eastern-Europe

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Introduction

The Internet has become globally one of the main sources of health-related information [1]. In the US, 59% of the adult population and 72% of the internet users have looked online for health information [2]. A European study on a representative sample including almost 8000 respondents from seven countries has shown that 44% of the total sample and 71 % of the internet users, resorted to the Internet to obtain health-related information [1]. Even though Romania was at the bottom of the European countries as far as the percentage of people using the internet to search for health-related information, 47% of the respondents did use the internet to obtain information about health and disease, according to a statistic published in 2014 [3].

While the Internet has been recognized as a useful educational resource not only for medical professionals but for consumers as well, a number of studies in the field of consumer health informatics have raised several reasons of concern, such as increased exposure of patients to incomplete, inaccurate, misguided or fraudulent health claims [4-6]. Misleading online information may have undesired consequences on the patients decision making [7] and there are some indications that even patients needing immediate critical care, such as those affected by stroke, may be exposed to potentially life-threatening information [8].

Although stroke is the second leading cause of mortality [9] and first cause of disability worldwide [9,10], the quality of online information about this condition has not been systematically evaluated.

The main objective of this study was to assess the quality of information about stroke on the Romanian and Hungarian websites in terms of completeness and accuracy.

Methods

The research was designed as an observational cross-sectional study. The sample included 25 Romanian and 25 Hungarian websites presenting information about stroke for the general public. The search procedure and selection steps are outlined in figure 1. Data acquisition and evaluation was performed during April-May 2018. General characteristics such as website ownership, main goal, website genre and medical approach were identified by the evaluators using a predetermined set of common instructions. The completeness and accuracy of the information were

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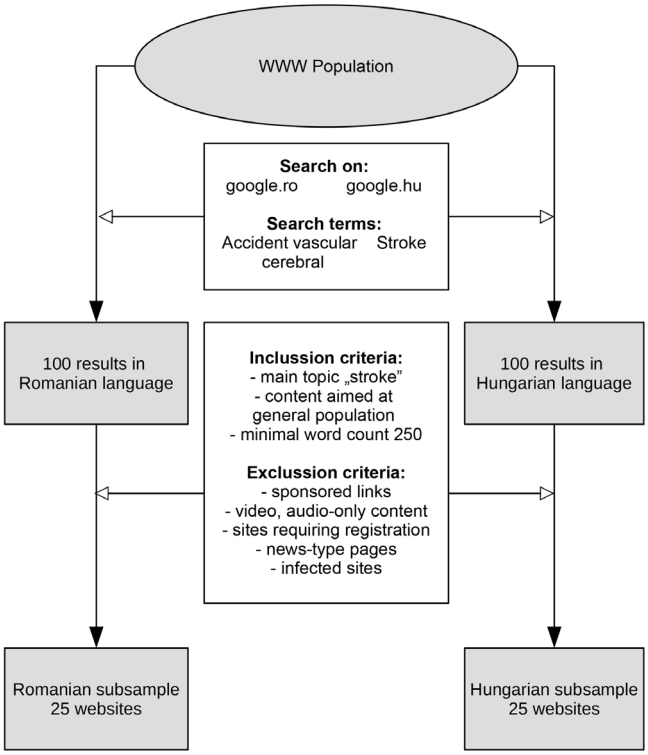

Fig. 1. Search procedure and selection of stroke-related Romanian and Hungarian websites

assessed by two independent assessors against a quality benchmark. The benchmark included 45 items considered relevant for laypersons interested about stroke and was developed from the evidence based literature (the benchmark is available upon request from the corresponding author). The items were reviewed by a neurologist with competence in health education. Completeness and accuracy scores were reported on a decimal scale (0 points meaning lowest quality, 10 points showing the highest quality). Completeness and accuracy scores were also computed separately for each of the main chapters of the topic (definition and epidemiology; symptoms and diagnostic; causes and risk factors; primary prevention; first aid and treatment). Selection procedures and assessment methodology are described in detail in previously published works by Nădăşan et al.[11-13].

Descriptive statistics and mean quality scores were calculated for each language sub-sample. Inter-rater agreement was assessed using Cohen's kappa test. Data were checked for normality using the Kolmogorov-Smirnov test. ANOVA test or t-test for independent samples were used as comparison tests for all data with normal distribution. All statistical analyses were performed in SPSS v. 22. The cut-off value for statistical significance was set at $\alpha = 0.05$.

Results

Overall, most of the websites were owned by private commercial companies (42%), had educational goal (66%), were designed as medical web-portals (46%) and had a conventional medicine approach (72%). The websites classification by general characteristics and language is presented in table I.

The mean relative completeness score of the whole sample (N=50) was 4.8 (SD=2.3) and the mean accuracy score was 6.6 (SD=0.9). Five of the websites had completeness scores equal to or above 8 points and 3 of the websites had accuracy scores equal to or above 8 points. Only 1 of the 50 websites had both completeness and accuracy scores above 8 points.

The Kolmogorov-Smirnov test has shown that all data had normal distribution, therefore we used parametric tests for comparison between subcategories. The quality scores of the investigated websites by language and the results of comparison tests between language sub-samples are presented in table II. Chapter specific completeness scores for all 50 websites as a whole, are presented in table III. The mean quality scores by general characteristic and the results of the comparison tests between website categories are presented in table IV.

Discussions

Overall, the Romanian and Hungarian websites presenting information about stroke for the general public may be characterized as poor. The observed completeness scores of the assessed websites, both Romanian and Hungarian, indicate that the users seeking information about stroke will find only about half of the information considered necessary for a thorough understanding of the topic they are interest in. The comparison test has shown that the mean completeness score of the Romanian stroke-related websites was statistically higher than that of the Hungarian websites (5.6 vs. 4.1 points out of 10; p=0.017), suggesting a relative superiority of the Romanian websites that might

Table I. Relative frequencies of the stroke-websites by general characteristics and language

General characteristics		Romanian (%) N=25	Hungarian (%) N=25
Ownership	Foundation, association	4	16
	Health service or product provider	36	24
	Commercial company	32	52
	Not identifiable	28	8
Main goal of the site	Educational	64	68
	Commercial	36	32
Site genre	Medical or general portal	40	52
	Online journal or magazine	24	20
	Online shop or company site	36	28
Medical approach	Conventional medicine	44	100
	Alternative or mixed	56	0

Table II. Comparisons of the completeness and accuracy scores by language sub-samples

Scores	Language	Mean (SD)	p-values
Relative Completeness Score	Romanian	5.6 (±1.9)	0.017[a]
	Hungarian	4.1 (±2.4)	
Relative Accuracy Score	Romanian	6.2 (±1.1)	0.020[a]
	Hungarian	7.0 (±0.7)	

[a]: t -test for independent samples; SD: standard deviation

Table III. Chapter specific relative completeness and accuracy scores

Stroke information chapters	Completeness score Mean (SD)	Accuracy score Mean (SD)
Definition and epidemiology	6.6 (±2.7)	5.9 (±2.3)
Symptoms and diagnostics	5.8 (±2.6)	8.5 (±2.2)
Causes and risk factors	5.1 (±3.0)	5.0 (±2.6)
Primary prevention measures	4.8 (±3.9)	5.8 (±3.6)
First aid and treatment	4.0 (±2.7)	6.1 (±2.8)

SD: standard deviation

be of relevance for the bilingual Transylvanian population from Romania. However, because the difference is very small and both scores remain well within a level that, realistically speaking, may be characterized as rather modest, the statistical difference does not translate into a practical, real-life advantage in terms of online documentation. In fact, the users' likelihood of landing on web-pages providing incomplete information about stroke remains very high no matter which of the two languages the users is familiar with.

The results regarding accuracy of online stroke-related information are slightly higher compared to those regarding completeness. While accuracy scores are less than one decimal point higher on average than completeness scores on the Romanian-language sites, the accuracy scores on the Hungarian-language sites are approximately three decimal points higher compared to the completeness scores. Although accuracy of the Hungarian stroke-related web-pages may be qualified as acceptable (7 points out of 10), and was found statistically significantly higher compared to the accuracy of the Romanian web-pages, advising bilingual users to rely preferentially on the information provided by the Hungarian language sites may not be warranted since these same Hungarian-language websites had poor ratings as far as completeness is concerned.

On one hand, the analysis of completeness and accuracy at the level of specific chapters has shown that most of the chapters had scores spread, as expected, around the mean values (4.8 and 6.6 respectively). On the other hand, the chapter-focused analysis revealed on the positive side that the section describing the symptoms of stroke had the highest score on accuracy (8.5 points out of 10), and on the negative side, the very chapter dealing with life-saving measures when suspecting a stroke-related emergency situation, recorded the lowest score on completeness (4 points out of 10).

Since the number of sites with consistently high scores (both scores above 8 points) was extremely low, users who search information about stroke on the Romanian and/or Hungarian websites may have a very high likelihood of being misinformed either because of the failure to obtain important information or because of being provided inaccurate information. Theoretically, the inconvenience of incomplete information could be mitigated by getting information from several sites with possibly complementary information. Practically, this strategy would require highly motivated users with ability to put together information obtained from several sources, and last but not least, it is time consuming.

The analysis of quality scores in relation to the general characteristic of the stroke-related websites has shown that completeness is not associated with any of the websites' characteristics. As far as accuracy, the tests have identified two characteristics that seem to be associated with websites accuracy (see table 4). Firstly, the websites owned by commercial companies had the highest accuracy scores (7 points out of 10) while those with unidentifiable ownership had the lowest accuracy score (6 points, out of 10). If future studies will confirm this association as being consistent on other topics besides stroke and also in other languages besides Romanian and Hungarian, users could be advised to check website ownership in order to get a clue about the quality of the information found on the respective web-page. Secondly, conventional medicine websites were associated with significantly higher accuracy scores (6.8 points out of 10) compared to alternative medicine websites, including websites with a mixed approach (5.9 points out ot ten). If confirmed, this association also might serve as friendly predictor of website accuracy for users with no medical background.

Table IV. Mean values of the relative completeness and accuracy scores by website general characteristics

General characteristics		RCS Mean (SD)	p-value	RAS Mean (SD)	p-value
Ownership	Foundation, association	3.8 (±2.9)	0.339[a]	6.5 (±1.2)	0.029[a]
	Health service or product provider	4.2 (±1.9)		6.4 (±1.0)	
	Commercial company	5.3 (±2.5)		7.0 (±0.8)	
	Not identifiable	5.2 (±2.0)		6.0 (±0.9)	
Main goal	Educational	5.0 (±2.4)	0.394[b]	6.6 (±1.0)	0.973[b]
	Commercial	4.4 (±2.1)		6.5 (±0.9)	
Site genre	Medical or general portal	5.3 (±2.6)	0.477[a]	6.6 (±0.9)	0.957[a]
	Online journal or magazine	4.6 (±2.0)		6.5 (±1.2)	
	Online shop or company site	4.4 (±2.1)		6.6 (±0.9)	
Medical approach	Conventional medicine	4.6 (±2.5)	0.382[b]	6.8 (±0.8)	0.002[b]
	Alternative or mixed	5.3 (±1.9)		5.9 (±1.1)	

RCS: relative completeness score; RAS: relative accuracy score; SD: standard deviation; [a]: ANOVA; [b]: t test for independent samples

Generally, the findings of this study are consistent with many other studies investigating the quality of online information about various medical conditions, both on the Romanian internet [11-15] as well as on the English, Spanish or other language websites [16-26]. With a few exceptions, most of the authors have reported modest completeness and accuracy scores but, it should be noted the heterogeneity of methodologies and evaluation tools applied in these studies prevents a rigorous comparison. As far as stroke-related information on the internet, the only study that evaluated the quality of information about this topic along with heart attack included a sample of Portuguese-language websites and concluded that the quality of online information on stroke was acceptable although frequently incomplete [27].

Strenghts and limitations

To the best of our knowledge, this is the first study assessing the quality of stroke-related information on the Romanian and Hungarian websites addressing the general population. The results of the study may provide individuals seeking information about stroke valuable insights on how to find the most complete and accurate online sources of information about stroke.

Another strength that merits to be highlighted is that we used two distinct scores to measure completeness and accuracy in contrast with most other tools which measure and report an overall score that does not distinguish quantitative and qualitative criteria. However, it is important to remember that the accuracy score, by design, measures only the correctness of the information presented on the website, and thus it should be interpreted only in relation with the completeness score.

Basically, the limitations of the study include those that are implicit to internet research. For example, the replication of the study might render different results due to: ongoing changes of the online content; using different search terms; using other search engines than Google. Another type of limitation that needs to be discussed is related to the subjective nature of the evaluators. It is known that ratings of the web-page content is somewhat dependent on the evaluators professional background [28]. In order to increase the level of objectivity of the assessment, the evaluations were performed by health professionals or medical students, all evaluators followed a common set of detailed instructions and, each website was assessed by two independent evaluators. After inter-grader agreement was statistically checked using Cohen's kappa test, a consensus evaluation was performed whenever it was necessary (kappa <0,8). Another limitation that should be clarified is the apparently small number of websites evaluated for each language. In this context, it should be pointed out that research on the users searching behavior has shown that the majority of internet users access only the websites included on the first page of the Google search results [29], therefore, the websites included in the present study covered the content browsed by most users with a generous margin of error. Finally, since our sample included only Romanian and Hungarian websites about stroke, the results of the study can not be generalized to other languages or other health-topics. In as much as Romanian and Hungarian educated users are visiting English websites for health-related purposes, it would be warranted that future studies assess the completeness and accuracy of these websites.

Conclusions

1. Overall, the information about stroke on the Romanian and Hungarian websites had poor and variable quality. Only half of the information considered necessary for a good understanding of stroke by users was present on the investigated sites.
2. Statistically, the completeness of stroke-related information on the Romanian language websites was significantly higher than on the Hungarian language websites, while the accuracy was significantly higher on the Hungarian-language websites. However, the differences were too small to offer a practical advantage to users of a particular language during online information seeking.
3. The completeness of stroke-related information was not associated with any of the general characteristics on the Romanian and Hungarian websites included in our sample. Although the accuracy of stroke-related information was associated with two of the investigated general characteristics, these associations need confirmation and must be interpreted with caution as far as their practical relevance.

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Authors' contribution

SDP – Conceptualization, data curation, formal analysis, investigation, project administration, writing original draft; Writing – review & editing)
AOP – Data curation, formal analysis, investigation, writing original draft, final approval
M Dănilă – Data curation, investigation, writing original draft, final approval
M Dobria – Data curation, writing original draft, final approval
DM – Data curation, writing original draft, final approval
VN – Conceptualization, formal analysis, methodology, supervision, visualization, writing review and editing

Conflict of interest

None to declare.

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CASE REPORT

Histopathological Diagnostic Criteria for Non-invasive Follicular Thyroid Neoplasm with Papillary-like Nuclear Features Highlighted by Six Illustrative Cases

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Introduction. The encapsulated, non-invasive subtype of follicular variant of papillary thyroid carcinoma (FVPTC) represents approximately 10% to 20% of all thyroid cancers. Many studies over the past decade have shown that these tumors carry an indolent clinical course, with no recurrence, even in patients treated by lobectomy. Their reclassification as neoplasms with "very low malignant potential" has recently been suggested by an international group of experts and a new terminology was proposed: "non-invasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP). However, a diagnosis of NIFTP is still challenging for many pathologists in daily practice. **Presentation of case series**. By presenting six illustrative cases of NIFTP, this article aims to highlight the diagnostic criteria and the burden difficulties when dealing with NIFTP cases. Characteristic histological features, inclusion and exclusion criteria for NIFTP, as well as sampling guidelines and differential diagnosis challenges are all discussed. **Conclusions**. The diagnosis of NIFTP is not straightforward and requires meeting strict inclusion and exclusion criteria. Total sampling of the tumor capsule in these cases is mandatory in order to exclude invasion (capsular and/or vascular). A diagnosis of NIFTP promotes a less-aggressive patient management that is, no need for completion thyroidectomy or radioactive iodine therapy.

Keywords: NIFTP, thyroid neoplasm, papillary thyroid carcinoma

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Introduction

Papillary thyroid carcinoma (PTC) is the most common thyroid malignancy, with a significant increasing incidence in the last four decades [1]. According to the growth pattern, two types of PTC are described: "conventional" PTC in which the architecture is manly papillary or mixed papillary and follicular, and the "follicular variant" of PTC (FVPTC) with a follicular growth pattern. This last variant was first described by Linsday in 1960 as a tumor with nuclear characteristics similar to those of PTC, a follicular growth pattern and a propensity for lymphatic and hematogenous spread similarly to PTC. Later on, it has been recognized that FVPTC has two distinct subtypes: encapsulated and infiltrative according to the presence/absence of encapsulation [2]. These 2 subtypes have clinically and genetically distinct characteristics [3-6]. Until recently, encapsulated FVPTCs were further classified into non-invasive and invasive subtypes according to the presence of tumor capsular or vascular invasion [6,7].

Many studies over the past decade have shown that non-invasive encapsulated FVPTCs carry an indolent clinical course and are not associated with tumor recurrence even in patients treated by lobectomy only [2,3,6-10]. Considering these, reclassification of non-invasive encapsulated FVPTC as a neoplasm with "very low malignant potential" has recently been suggested by an international group of specialists in thyroid pathology. A new terminology was proposed: "non-invasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) [11]. NIFTP is now considered a distinct category and was also included in the new WHO (World Health Organization) Classification of *Tumors of Endocrine Organs* 2017 [12]. The introduction of NIFTP represents a significant paradigm shift in thyroid pathology and is thought to have a major impact in the diagnosis and treatment of thyroid neoplasms [13].

However, a diagnosis of NIFTP is still challenging for many pathologists in daily practice. By presenting six illustrative cases of NIFTP, this article aims to highlights the diagnostic criteria and the difficulties when dealing with NIFTP cases. Characteristic histological features, inclusion and exclusion criteria for NIFTP, as well as sampling guidelines and differential diagnosis challenges are all discussed.

Presentation of case series

Patients

All the cases included in the study were retrieved from the files of the Department of Pathology, Tîrgu-Mureş County Hospital, between May 2016 and February 2018.

Written informed consent was obtained from all patients included in this study. The Ethics Committee of the University of Medicine and Pharmacy of Tîrgu-Mureş approved the study.

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Table I. Demographical and pathological characteristics for the study cases.

	Age/ Sex	Extent/ type of surgery	Tumor location	Microscopical features							
				Tumor size (mm)	Multi-focality	Encapsulation/ well demarcation	Capsular ±vascular invasion	Growth pattern (predominat)	Other growth patterns (%)	Intra-tumoral fibrosis	Nuclear score*
Case no. 1	42/F	TT	LTL	17	no	well demarcated by thin or partial capsule	absent	microfolicular	solid (20%)	absent	3
Case no. 2	38/F	TT	LTL	20	no	encapsulated, thick capsule	absent	microfolicular	-	absent	2
Case no. 3	31/F	LL	LTL	20	no	encapsulated, thick capsule	absent	microfolicular	solid/trabecular (20%)	present	2
Case no. 4	41/F	TT	LTL	27	no	well demarcated by a thin or partial capsule	absent	micro- and normofolicular	solid (20%)	absent	2
Case no. 5	27/F	LL	LTL	11	no	well demarcated by a thin or partial capsule	absent	microfolicular	solid (20%)	present	3
Case no. 6	48/F	TT	LTL	15	no	well demarcated by a thin or partial capsule	absent	microfolicular	trabecular/ solid (20%)	present	2

Legend Table I: TT: Total Thyroidectomy; LL: Left lobectomy; LTL: Left Thyroid Lobe.

*Score 2: evidence of at least two of the following characteristic nuclear features: (1) size and shape (enlargement/overlapping/ crowding, elongation), (2) membrane irregularities (irregular contourus, grooves, pseudoinclusions) and (3) chromatin characteristics (clearing and margination/glassy nuclei). Score 3: evidence of all three nuclear features categories mentioned above.

Demographical and pathological characteristics for the study cases are summarized in Table I.

Results

All patients were females, aged between 27 to 48 years-old, who had been admitted to hospital for a cold, hypoechoic, solitary thyroid nodule. Four cases involved total thyrodectomy; in the other two cases, left lobectomy was performed. Tissue samples were sent to the Department of Pathology.

Histopathological analysis of the tissue samples

The surgical specimens were all fixed in 10% buffered formaldehyde for between 48 to 72 hours, depending on the size of the specimen. The tumors were entirely sampled and further processed according to routine practice guidelines, which included dehydration, clearing and paraffin embedding.

Five-µm-thick sections were stained with hematoxylin-eozine (HE) and examined by two pathologists (ANB, AB), independently and then together by a double-headed microscope.

Pathological features (Table I)

In all cases, a well-delimited, solitary, compact, gray-whitish nodule was described, with a maximal diameter ranging between 11 to 27 mm.

In two cases, the nodules were clearly encapsulated, with evidence of a thick, calcified capsule surrounding the nodule (Figure 1A). In the other four cases encapsulation was described as being very thin or partial capsule (Figure 1B). In all six cases, however, there was a sharp interface between the tumor and remaining parenchyma. No signs of capsular or vascular invasion were observed following sampling of the entire tumor nodules and multiple sections evaluation. The predominant architectural pattern was micro-follicular (Figure 1C). In five cases solid, trabecular growth patterns were also present (Figure 1D), but represented less than 30% of the tumor area. The nuclei revealed discrete, incomplete characteristic of PTC nuclear features. They were minimally to moderately enlarged with nuclear membrane irregularities, including groves or indentations, or nuclear clearing.

Three cases met two of the three nuclear criteria, and the remaining three met all three nuclear criteria for NIFTP (Figure 2A, B) (Figure 2C, D).

All cases were consistent with a diagnosis of "non-invasive follicular thyroid neoplasm with papillary-like nuclear features", based on the following criteria, in accordance with Nikiforov et al. (11):

- encapsulation/ well demarcation of the tumor's interface from the adjacent thyroid parenchyma.
- absence of invasion (capsular and/or vascular) following entire sampling of the tumor capsule and multiple sections evaluation.
- dense, microfollicular growth pattern of the tumor, with the solid growth component, if present, represented less than 30%.
- focal characteristic PTC nuclear changes, alternating with areas in which the nuclear changes were only discrete and incomplete and a nuclear score of 2-3.

Discussion

The encapsulated, non-invasive subtype of FVPTC accounts for up for 10% to 20% of all thyroid cancers in Europe and North America [14].

In 2016 a new terminology for these tumors was proposed by Nikiforov et al. (11) who suggested they be reclassified as neoplasms with "very low malignant potential". Clinically, this reclassification is expected to have many consequences including a decrease in the number of PTCs, a decrease in complications due to total thyroidectomy or RAI, a reduction in medical expenses and a significant reduction in the psychological and social stress associated with the word "cancer" on patients.

However, it is essential that the diagnosis of NIFTP, as detailed by Nikiforov et al. [11] is determined accurately, as this will dictate a different therapeutic approach compared to PTC or other types of thyroid cancer [15].

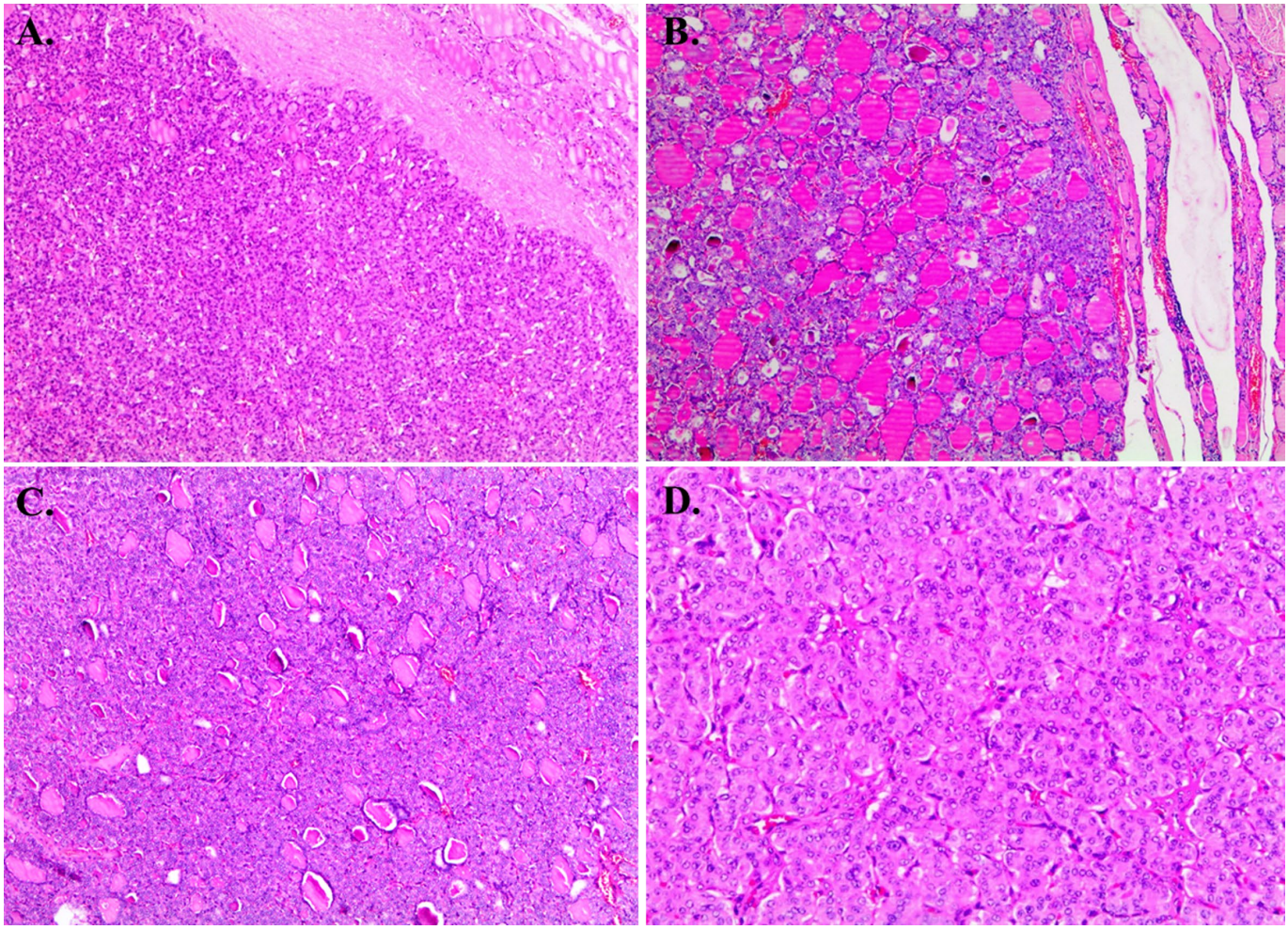

Fig. 1. Diagnostic criteria for non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP): encapsulation (A, 4x) or clear demarcation by a very thin, partial capsule (B, 4x) with no signs of capsular or vascular invasion; follicular architecture with a predominant microfollicular growth pattern and no papillae (C, 4x); solid, trabecular growth patterns can also be present, but these areas should represent less than 30% of the tumor (D, 10x).

Tumors designated as NIFTP are required to meet strict inclusion and exclusion criteria.

Inclusion criteria are:

– size of the tumor more than 1 cm, with encapsulation or clear demarcation.
– follicular growth pattern.
– a nuclear score 2-3.

Nikiforov et al. developed a simple and reproducible nuclear scoring system that could assist in the diagnosis of NIFTP in every-day practice [11]. The characteristic PTC nuclear features were separated into three main categories: (1) size and shape (enlargement/overlapping/crowding, elongation), (2) membrane irregularities (irregular contours, grooves, pseudoinclusions) and (3) chromatin characteristics (clearing and margination/glassy nuclei). Each class of nuclear features was given a score of 0 or 1 resulting in a range of scores from 0 to 3.

In our series, three cases were consistent with a nuclear score of 2, and three cases fulfilled all criteria and were consistent with a nuclear score of 3.

Exclusion criteria are:

– true papillae >1%. (2)
– psammoma bodies.
– capsular or vascular invasion.
– tumor necrosis.
– high mitotic activity.
– >30% solid/trabecular/insular growth pattern.
– size of the tumor ≤1 cm.

By applying these criteria conventional PTC (true papillae >1% and psammoma bodies), invasive subtype of encapsulated FVPTC (capsular and/or vascular invasion) and poorly differentiated thyroid carcinoma (tumor necrosis and high mitotic activity) are excluded [16].

Since previous studies have evaluated only tumors larger than 1 cm, tumors below 1 cm should not be classified as NIFTPs, but as papillary thyroid micro-carcinomas. Addressing issues of diagnosis, a recent monograph [17] provides a synopsis and guide for pathologists on NIFTP and focuses on histologic features, including inclusion and exclusion criteria used to define NIFTP, as well as grossing guidelines, reporting practices, and potential diagnostic limitations.

Conclusions

The introduction of the terminology NIFTP represents a significant paradigm shift in thyroid pathology. Herein, we

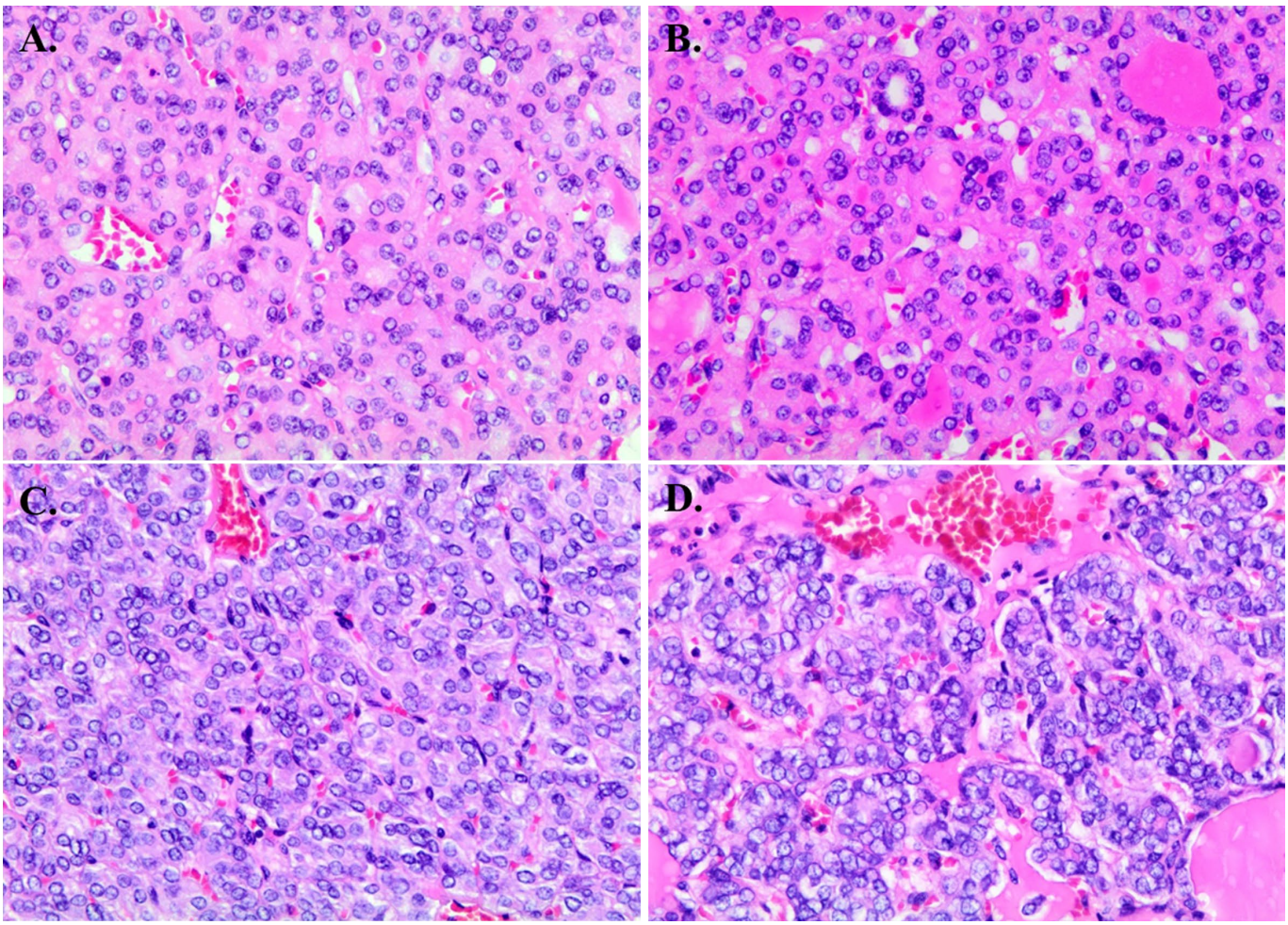

Fig. 2. Nuclear features of non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). A nuclear scoring system can be utilized in evaluating NIFTP. Nuclear features are grouped in three categories (1) size and shape (enlargement/overlapping/ crowding, elongation); (2) membrane irregularities (irregular contourus, grooves, pseudoinclusions) and (3) chromatin characteristics (clearing and margination/glassy nuclei). For each feature, a tumour can receive one point, such that a tumour can score a total of 0-3 points. Eg: a tumour consisting with score 2 (A, B, 40x) and a tumour consisting with score 3 (C, D, 40x).

report the first six cases of NIFTPs diagnosed in our department since the introduction of the new terminology. Labeling these lesions as tumors, rather than carcinomas reflects more accurately their biologic potential and promotes less-aggressive patient management. It follows that there is no need for completion thyroidectomy or radioactive iodine therapy.

However, the term NIFTP has been proposed for lesions meeting strict inclusion and exclusion diagnostic criteria. Total sampling of the tumor capsule in these cases is mandatory in order to exclude capsular or vascular invasion.

Conflicts of interest

The authors declare no conflicts of interest.

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CASE REPORT

Glomus Tumor of the Kidney: Case report

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Introduction: Glomus tumors are rare benign mesenchymal neoplasms accounting for only 2% of all types of soft tissue tumors. Commonly located in the peripheral soft tissues, they are most frequently encountered in the subungual areas of fingers and toes, and very rarely in visceral organs due to the absence of glomus bodies. To date, 22 cases of primary renal glomus tumors have been described in the literature, of which 17 benign, with no evidence of recurrence or metastasis, three cases of malignant glomus tumor, and two cases with uncertain malignant potential. **Case report**: We report the 18th case of a benign glomus tumor of the kidney in a 49-year-old female patient, presenting the microscopic appearance (round, uniform cells with indistinct borders, scant finely granular eosinophilic cytoplasm, round nuclei lacking prominent nucleoli, arranged in solid sheets, accompanied by slit-like vascular spaces), the immunohistochemical profile (tumor cells showed immunoreactivity for smooth muscle actin, vimentin, as well as for CD34; they were negative for AE1/AE3, desmin, HMB-45, S-100 protein, renin, and chromogranin), and the differential diagnosis of this rare entity (juxtaglomerular tumor, angiomyolipoma, hemangioma, epithelioid leyomioma, solitary fibrous tumor, carcinoid tumor, and paraganglioma). **Conclusion**: Primary renal glomus tumors are rare tumors that radiologically can mimic other mesenchymal renal neoplasm. Accurate diagnosis is based on the microscopic appearance and especially the characteristic immunophenotype.

Keywords: glomus tumor, kidney tumor, immunohistochemistry

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Introduction

Glomus tumors are rare benign mesenchymal neoplasms which account for only 2% of all soft tissue tumors. They originate from glomus bodies which are neuroarterial receptors with an essential role in thermoregulation [1]. Glomus tumors usually occur in the peripheral soft tissues, most frequently in the subungual areas of fingers and toes, and rarely in visceral organs due to the absence of glomus bodies [1, 2].

To date, 22 cases of primary renal glomus tumors have been described in the literature, of which 17 benign, with no evidence of recurrence or metastasis, three cases of malignant glomus tumor, and two cases with uncertain malignant potential [3-14]. We report the 18th case of a benign kidney glomus tumor, presenting the microscopic aspect, the immunohistochemical profile, and the differential diagnosis of this rare entity.

Case report

Our 49-year-old female patient presented to the hospital with abdominal discomfort, without any other associated symptoms such as radiating pain, weight loss or hematuria. CT scan revealed a 4 cm heterogeneous mass in the renal parenchyma, suggesting a renal cell carcinoma, for which she subsequently underwent total nephrectomy. Macroscopically, the tumor was encapsulated, compact, and tan-grey in color, with a thin capsule which was visible on microscopy (Figure 1A). The cells displayed a solid sheet arrangement and were surrounded by slit-like vascular spaces (Figure 1B). They were round, uniform, cell borders were indistinct, with a scant finely granular eosinophilic cytoplasm and round nuclei lacking prominent nucleoli (Figure 2A). There was no evidence of pleomorphism, necrosis, increased mitotic activity of more than 2/50 high power field and atypical mitoses. Capsular and lymphovascular invasion were not noticed. Tumor cells were immunoreactive for vimentin, smooth muscle actin (Figure 2B), but also for CD34 (Figure 2C). They were negative for AE1/AE3 (Figure 2D), desmin, HMB-45, S-100 protein, chromogranin, and renin. Morphological and immunohistochemical assessment prompted a diagnosis of primary solid glomus tumor of the kidney. The patient is free of disease six years after nephrectomy. Informed consent was obtained from the patient.

Discussion

The first record of glomus tumors dates back to 1924 when Masson described perivascular mesenchymal neoplasms comprising cells which resembled modified smooth muscle cells of normal glomus bodies [15]. Although glomus tumors are characteristically located on the distal extremities and appear as small, red-blue, solitary, and painful nodules, few cases of such primary tumors have been described in the visceral organs: oral cavity, sinonasal region, larynx, trachea, lung, mediastinum, gastrointestinal tract, pancreas, liver, female genital tract, and bone [2].

Glomus tumors are rare in the kidney, with the first case reported in 1957 [5].Since then, only 22 cases have been described, of which 15 men and 7 women, with patient ages ranging from 17 to 81[2-14, 16-18].

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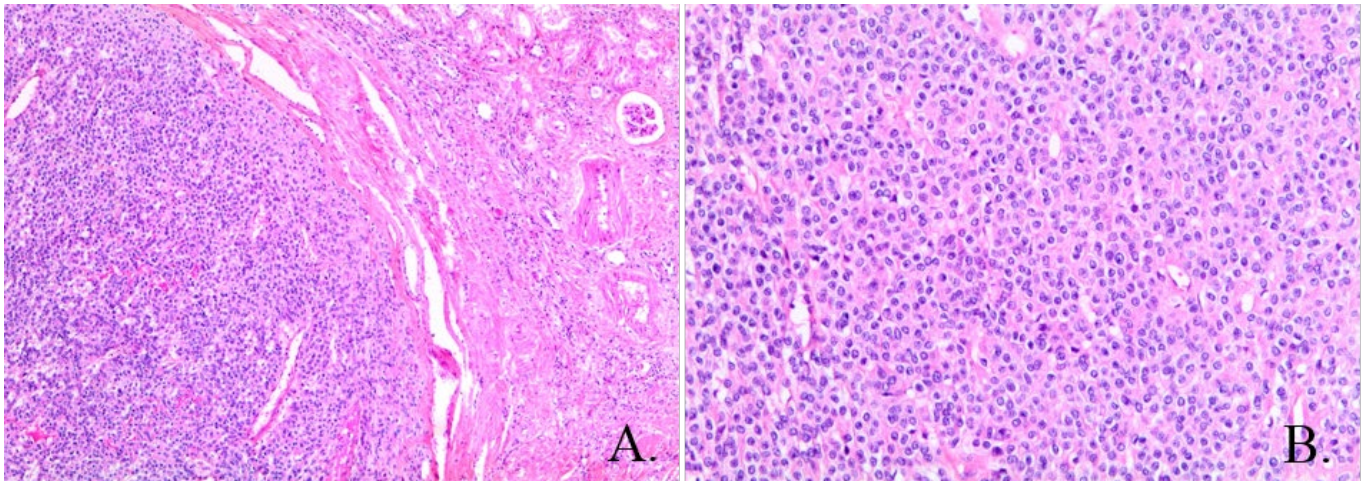

Fig. 1. A - A well-defined, encapsulated tumor, situated in the renal parenchyma (4x); B - Tumor cells arranged in solid sheets, accompanied by slit-like vascular spaces (10x).

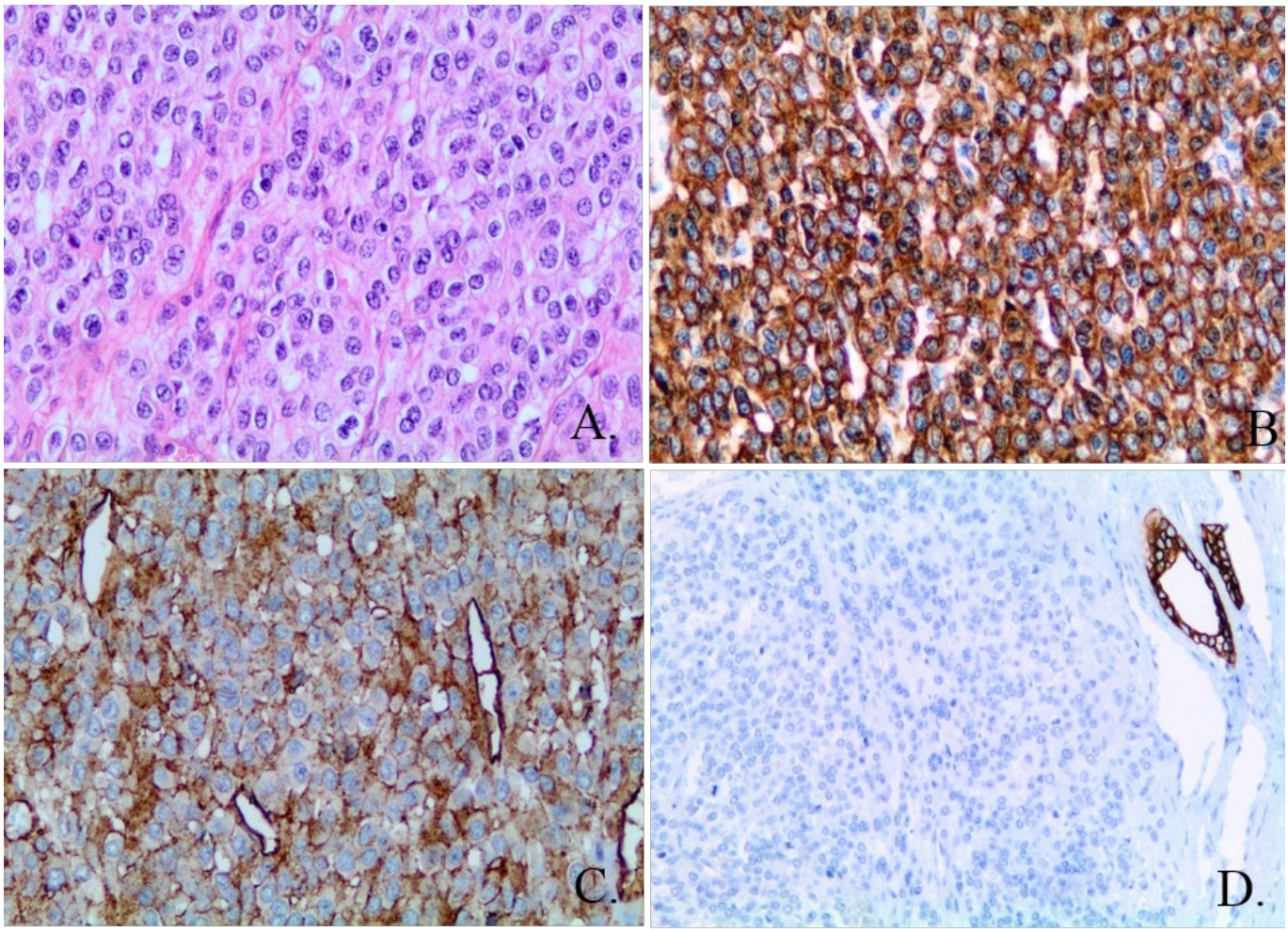

Fig. 2: A - On high magnification, cells are round, uniform, have indistinct cell borders, scant finely granular eosinophilic cytoplasm, round nuclei without prominent nucleoli (20x); B - Smooth muscle actin is strongly positive in the tumor cells (20x); C - CD 34 is expressed by the tumor and endothelial cells (20x); D - AE1/AE2 is negative in the tumor cells and positive in the epithelium of the tubes (20x).

The majority of these tumors are discovered incidentally during imaging examinations, because the clinical presentation is nonspecific, with symptoms such as flank and abdominal pain, and microscopic hematuria. Due to the lack of characteristic radiological findings, the preoperative diagnosis of glomus tumors is difficult.

For a definitive diagnosis, histological examination and immunohistochemical staining are mandatory. Generally, such tumors are composed of round ovoid epithelioid glomus cells, blood vessels, and smooth muscle cells [1].They can be subcategorized as solid glomus tumors, glomangiomas, or glomangiomyomas based on the prevalence of one of the above mentioned components. Solid glomus tumors represent 75% of cases and are composed of nests of glomus tumor cells surrounding capillary sized vessels, in some cases with a hyaline or myxoid stroma. Glomangiomas are

composed of cavernous hemangioma-like structures surrounded by glomus cells and represent 20% of cases. In much rarer cases of glomangiomyomas, a transition from typical glomus cells to elongated cells resembling mature smooth muscle can be observed [1, 8].

Although they are epithelioid in appearance and are closely associated with vessels, glomus cells do not express any epithelial (cytokeratin and EMA) marker, but they stain intensely with smooth muscle actin, common muscle actin, and vimentin. Tumor immunoreactivity for desmin is variable, ranging from no expression to only focal positivity. CD 34 positivity is significantly stronger in peripheral glomus tumors compared with visceral ones. In our case, CD34 was positive as in the cases described by Al-Ahmadie et al. and Gravet C et al. [5, 8].

Although the majority of glomus tumors are benign, some malignant cases have also been described as very aggressive tumors. Because of tumor progression, most patients with malignant glomus tumors in the visceral organs die shortly after diagnosis [16-18]. Folpe et al. analyzed 52 cases of atypical glomus tumors of the peripheral soft tissue in order to establish criteria of malignancy, suggesting the following: size (more than 2 cm), subfascial or deep location, atypical mitotic figures, moderate to high nuclear grade, and mitotic activity (5 mitoses/50high-power fields) [19].

Lamba et al. described the first aggressive metastatic malignant glomus tumor in the kidney with distal organ metastases and no response to chemotherapy, a tumor which was in line with the criteria suggested by Folpe et al. [16]. In a recent study, Li R et al. confirmed the malignant potential, reporting one case of metastatic glomus tumor, 7 years after the initial diagnosis and also a glomus tumor with uncertain malignant potential with tumor thrombus in the renal vein and the inferior vena cava [18].

If the differential diagnosis from epithelial tumors of the kidney is relatively easy, their differentiation from other non-epithelial renal tumors may be difficult, frequently requiring immunohistochemical staining. One of the most important differential diagnosis is made with juxtaglomerular tumor, but it should also include angiomyolipoma, hemangioma, epithelioid leyomioma, solitary fibrous tumor, carcinoid tumor, and paraganglioma.

Juxtaglomerular cell tumor is associated with excessive renin secretion. Patients experience severe and poorly controlled hypertension and hyperkalemia in combination with high plasma renin levels. Although it may present overlapping morphological characteristics with glomus tumors, it may also exhibit a tubular and/or papillary architecture. The cells contain renin granules which can be highlighted by immunohistochemistry with antibodies to renin [20].

Angiomyolipoma, the most common mesenchymal tumor of the kidney, can be considered in the differential diagnosis of glomus tumor in cases with a predominant muscular component. Proper sampling and careful examination will prove the presence of adipose tissue, blood vessels, and smooth muscle, the three components of angiomyolipoma. Perivascular epithelioid cells can be highlighted by immunohistochemistry with HMB-45 and Melan A [21].

Capillary or, more commonly, cavernous renal hemangiomas are fairly rare tumors which are composed of blood vessels of different sizes containing blood, lined by endothelial cells. These vessels lie in a hyalinized stroma containing red blood cells and hemosiderin deposits. Since the vessel walls of these tumors may focally contain smooth muscle, although not being a predominant pattern, it should be differentiated from a glomus tumor [21, 22].

Epithelioid leiomyomas of the kidney are also rare and consist of bundles of smooth muscle positive for desmin, but, unlike glomus tumors, they lack the intimate relationship with blood vessels [21].

Hemangiopericytoma is a proliferation of cells with slight variability in cellularity, having a "staghorn" vascular pattern with packed pericytes around a vascular endothelium and minimal collagenization which can be variable vary both in size and shape. Immunohistochemically, the tumor cells are positive for CD31, CD34, CD99, S-100, vimentin, cytokeratin, and negative for smooth muscle actin, unlike glomus tumor [23].

Solitary fibrous tumors present a pattern similar to a hemangiopericytoma with a typical spindle or oval cell proliferation. The cells are arranged in a storiform and fascicular pattern in a hyalinized stroma. They are positive for CD34 [21, 23].

Carcinoid tumors have morphological features similar to carcinoid tumors encountered in other organs, i.e. trabeculae intertwined between nests of monotonous cuboidal cells which show "salt and pepper" nuclear appearance. The tumor cells stain positive for keratin 18, synaptophysin, chromagranin, and CD56 [24].

Paraganglioma is composed of tumor cell nests arranged in a Zellballen pattern and having a highly vascularized fibrous stroma. Immunohistochemically, it typically expresses synaptophysin and chromogranin and contains sustentacular cells positive for S100 [2].

Conclusion

We report the 18th case of a benign glomus tumor of the kidney. Primary renal glomus tumors are rare tumors that radiologically can mimic other mesenchymal renal neoplasm. Accurate diagnosis is based on the microscopic appearance and especially the characteristic immunophenotype.

Acknowledgment

The present case was previously reported as a poster presentation at the 26th European Congress of Pathology (ECP 2014), 30 August – 3 September 2014, London, United Kingdom.

Authors' contribution

ED – Conceptualization, resources, writing original draft, writing review and editing
AL – Conceptualization, methodology, resources, writing original draft, writing review and editing
TT – Conceptualization, methodology, resources; writing original draft, writing review and editing
AN – Writing original draft, writing review and editing
AB – Conceptualization, supervision, validation, writing original draft, writing review and editing

Conflict of interest

None to declare

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