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ORIGINAL ARTICLE

Basic Study

Reliability of Sawai's classification for dental cervical abrasions: A pilot study

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Institutional review board statement: As this study did not involve any diagnostic or treatment procedure on the patient, it did not require any institutional ethical clearance.

Informed consent statement: This study involved the use of photographs of patients' dentition only. Patients who voluntarily agreed to allow their dental photographs to be taken were included in the study. Their informed consent was obtained.

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Abstract

AIM

To test the reliability of the Sawai's classification for dental cervical abrasions.

METHODS

Intraoral photographs of 70 teeth from 23 patients with tooth abrasions were taken by the first examiner MS. The teeth were marked and the photos were maintained in a soft copy sequentially. Two other examiners FA and SC were trained in the use of the classification and any clarifications needed were provided at the beginning of the study. Each examiner was then given the soft copy of the complied photographs and was asked to classify the dental cervical abrasion according to their understanding of the Sawai's classification. They were given sheets to write their responses for every marked tooth. All the examiners were blinded to each other's observations which were then tested for inter-rater agreement among the three examiners.

RESULTS

The 70 teeth with tooth abrasions from 23 patients were examined by 3 investigators (MS, FA and SC) to test the reliability of the Sawai's classification system for tooth abrasion. Each examiner marked their responses in separate sheets which were blinded to each other. The kappa statistics were performed for inter-rater agreement among the three examiners. The level of agreement was evaluated according to the six-level nomenclature given by Landis and Koch. ICC and 95%CI between two examiners, *i.e.*, the inter-rater agreement among

1st examiner (MS) and 2nd examiner (FA) was 0.89. The inter-rater agreement among 1st examiner (MS) and 3rd examiner (SC) was 0.89. And the inter-rater agreement among 2nd examiner (FA) and 3rd examiner (SC) was 0.83. All the three comparisons show an almost perfect agreement between them.

CONCLUSION

There is an almost perfect agreement between multiple observers for classifying dental cervical abrasions using Sawai's classification. Hence, this classification is reliable.

Key words: Tooth abrasion; Classification; Diagnosis; Tooth wear; Dental education; Diagnostic techniques and procedures

Core tip: Currently, an ideal index for tooth abrasion is lacking. The available indices are either too time consuming or complicated. Hence, an easy and least time-consuming classification was proposed. The present study evaluates the reliability of the Sawai's classification. In this study, out of three observers, two were students of dentistry (undergoing internship). The study shows that there was almost perfect agreement amongst the observers in classifying the tooth abrasions. Also, it was noted that the classification was easy to understand and use and least time consuming. So the authors suggest that this classification can be effectively used in daily dental practice.

Sawai MA, Daing A, Adeel F, Chawla S. Reliability of Sawai's classification for dental cervical abrasions: A pilot study. *World J Clin Cases* 2017; 5(12): 407-411 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i12/407.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i12.407

INTRODUCTION

Tooth wear is a modern day problem. It produces varying symptoms ranging from discomfort, pain and also may lead to loss of tooth vitality. As dentists, we need to diagnose and monitor tooth loss and provide adequate treatment to our patients. Though, a lot of emphasis has been given towards treatment aspect of cervical abrasions, much research is required to develop a comprehensive method to diagnose and classify cervical abrasions. Different indices have been given in the past to diagnose and grade the cervical abrasions. For example: Eccles index for dental erosion of non-industrial origin[1], Smith and Knight's Tooth Wear Index[2] and Erosion Index by Lussi[3]. Bardsley *et al*[4] pioneered a new, simplified version of tooth wear index (TWI) and Khan *et al*[5] reported cervical lesions of different morphological types. Across the world, qualitative and quantitative methods were used to measure cervical abrasion. Although these grading methods are available, they still lack objective measurements. Some methods rely on clinical descriptions and others on physical measurements. There is a lack of uniformity and hence comparison of data is difficult. An ideal index is hence needed to scientifically diagnose the disease. A classification system is necessary in order to provide a framework to scientifically study the etiology, pathogenesis and treatment of diseases in an orderly fashion. In addition, such systems give clinicians a way to organize the health care needs of their patients[6]. The already available classification systems for dental cervical abrasion have limitations as some of them are descriptive and others are time consuming. A simple classification system was proposed by Sawai in 2014[7].

The present study was conducted to test the reliability of Sawai's classification system[7] for Dental Cervical Abrasions.

MATERIALS AND METHODS

Individuals showing at least one dental cervical abrasion were recruited for the study to check the reliability of this new classification. The patients were recruited from the Out-Patient Department of Department of Periodontology, Faculty of Dentistry, Jamia Millia Islamia, NewDelhi, India and signed a written informed consent in accordance with Helsinki declaration of 1975 as revised in 2000.

Inclusion criteria including: (1) the presence of dental cervical abrasion on one or more teeth; and (2) completion of cause-related therapy when necessary. Exclusion criteria were patients who did not want to participate voluntarily.

Assessment of agreement

The subjects were recruited by the first examiner (MS) and photographs of the teeth with dental cervical abrasion were taken and teeth were marked. The photographs were sequenced and maintained in a soft copy. The other two examiners (FA and SC) were trained on the use of this classification system. All clarifications were provided before the start of the study. Each examiner was then given the soft copy of the compiled sequence of photographs and a sheet to write their responses. The examiners classified the tooth wear defect according to the Sawai's classification[7].

Each examiner used sufficient time to classify every defect. All the three examiners were blinded to the evaluation of each other. The results were then analyzed statistically to test the reliability of the classification.

Statistical analysis

Variables were reported as mean ± standard deviation (SD) for continuous variables or frequency and percentage for discreet variables unless otherwise specified. Kappa statistics were performed for 70 observations to analyze inter-rater agreement amongst the three examiners.

Table 1 MS photography based evaluation and FA photography based evaluation Crosstab

		FA photography based evaluation								Total	Measure of agreement, χ value
		Class A			Class B			Class C			
		Type Ⅰ	Type Ⅱ	Type Ⅲ	Type Ⅰ	Type Ⅱ	Type Ⅲ	Type Ⅰ	Type Ⅱ		
MS Photography based evaluation	Class A Type Ⅰ	12	0	0	0	0	0	0	0	12	0.899
	Class A Type Ⅱ	1	10	0	0	1	0	0	1	13	
	Class A Type Ⅲ	0	0	4	0	0	0	0	0	4	
	Class B Type Ⅰ	0	0	0	2	0	0	0	0	2	
	Class B Type Ⅱ	0	0	0	0	9	0	0	0	9	
	Class B Type Ⅲ	0	0	0	0	0	7	0	0	7	
	Class C Type Ⅱ	0	0	0	0	0	2	6	0	8	
	Class C Type Ⅲ	0	0	0	0	0	1	0	14	15	
Total		13	10	4	2	10	10	6	15	70	

Table 2 MS photography based evaluation and SC photography Crosstab

		SC photography								Total	Measure of agreement, χ value
		Class A			Class B			Class C			
		Type Ⅰ	Type Ⅱ	Type Ⅲ	Type Ⅰ	Type Ⅱ	Type Ⅲ	Type Ⅰ	Type Ⅱ		
MS Photography based evaluation	Class A Type Ⅰ	12	0	0	0	0	0	0	0	12	0.899
	Class A Type Ⅱ	0	11	0	0	0	0	2	0	13	
	Class A Type Ⅲ	0	0	3	0	0	0	0	1	4	
	Class B Type Ⅰ	0	0	0	2	0	0	0	0	2	
	Class B Type Ⅱ	0	0	0	0	8	0	1	0	9	
	Class B Type Ⅲ	0	0	0	0	0	6	1	0	7	
	Class C Type Ⅱ	1	0	0	0	0	0	7	0	8	
	Class C Type Ⅲ	0	0	0	0	0	0	0	15	15	
Total		13	11	3	2	8	6	11	16	70	

SPSS version 17 (SPSS, Inc., Chicago, IL, United States) was used for data analysis.

The level of agreement was evaluated according to the six-level nomenclature given by Landis and Koch[8]: (1)Poor agreement: 0.00; (2) Slight agreement: 0.00-0.20; (3) Fair agreement: 0.21-0.40; (4) Moderate agreement: 0.41-0.60; (5) Substantial agreement: 0.61-0.80; and (6) Almost perfect agreement: 0.81-1.00.

RESULTS

A total 70 observations from 23 patients were examined by 3 investigators (MS, FA and SC) to test the reliability of the Sawai's classification[7] system for tooth abrasion. The kappa statistics were performed for inter-rater agreement among the three examiners. ICC and 95%CI between two examiners, *i.e.*, the inter-rater agreement among 1st examiner (MS) and 2nd examiner (FA) was 0.89 (Table 1). The inter-rater agreement among 1st examiner (MS) and 3rd examiner (SC) was 0.89 (Table 2). And the inter-rater agreement among 2nd examiner (FA) and 3rd examiner (SC) was 0.83 (Table 3). All three comparisons show an almost perfect agreement amongst the three observers.

DISCUSSION

In dentistry, classifications are widely used to categorize defects or diseases based on their etiology, diagnosis, treatment and prognosis. A "Classification" is defined as "systematic arrangements in groups or categories according to established criteria[9]."

There are many classifications available for tooth wear. The earliest known index is by Broca[10], 1879 for tooth attrition. It was followed by index given by Restarski *et al*[11] in 1945 which evaluated the severity of erosive destruction using the 6 point grading system. But concerns were raised regarding its reproducibility.

The commonly known Eccles's index[1] was given in 1979 initially classified the lesions into early, small and advanced types. It was refined and expanded in 1982 with more descriptive criteria; grading both severity and site erosion due to non-industrial causes. It is considered as one of the cardinal indices from which others have evolved[4].

Later, Xhonga and Valdimanis[12] divided erosions into four levels by measurement with a periodontal probe: none, minor, moderate and severe. They further differentiated the types of erosion by morphological descriptions, such as wedge, saucer, groove and atypical. However, they did not address the problem of inter- or intra-examiner variability.

Other index like Smith and Knight's Tooth Wear Index (TWI)[2] was given in 1984 which was a comprehensive system and was more clinically relevant. It produced results from intra- and inter-rater reproducibility within an acceptable range. It could be used on study models and photographs also. However, it was very time consuming

Table 3 FA photography based evaluation and SC photography Cross tabulation

		SC photography								Total	Measure of agreement, χ value
		Class A			Class B			Class C			
		Type Ⅰ	Type Ⅱ	Type Ⅲ	Type Ⅰ	Type Ⅱ	Type Ⅲ	Type Ⅰ	Type Ⅱ		
MS Photography based evaluation	Class A Type Ⅰ	12	0	0	0	0	0	1	0	13	0.832
	Class A Type Ⅱ	0	9	0	0	0	0	1	0	10	
	Class A Type Ⅲ	0	0	3	0	0	0	0	1	4	
	Class B Type Ⅰ	0	0	0	2	0	0	0	0	2	
	Class B Type Ⅱ	0	1	0	0	8	0	1	0	10	
	Class B Type Ⅲ	1	0	0	0	0	6	2	1	10	
	Class C Type Ⅱ	0	0	0	0	0	0	6	0	6	
	Class C Type Ⅲ	0	1	0	0	0	0	0	14	15	
Total		13	11	3	2	8	6	11	16	70	

and always required computer assistance as the amount of data generated was very high.

Linkosalo and Markkanen[13] used a quantitative, four-scale grading system for severity relating to involvement of dentine. This index was modified by Lussi *et al*[3]. Later, Bardsley *et al*[4] carried out epidemiological studies on adolescents in North West England using a new, simplified version of TWI. It collected data from 40 surfaces from every subject. However, despite calibration and training, there were difficulties in diagnosing dentine exposure in epidemiological field.

Larsen *et al*[14] recommended a new clinical index. It was based on clinical examination, photographs and study casts. Each tooth surface was scored, with six grades of erosion severity modelled using Smith and Knight's TWI; however its criteria is complicated and time consuming.

Thus, there was a need of new classification system for tooth wear which was proposed by Sawai[7] in 2014. The present study evaluated the sensitivity of using this classification system by three observers.

An ideal classification should have following characteristics according to the criteria given by Murphy[15] in 1997: (1) Naturalness; (2) Usefulness; (3) Simplicity; (4) Exhaustiveness; (5) Disjointness; and (6) Constructability.

When this proposed classification is tested for these qualities of an "Ideal Index", it is seen that this system is simple, exhaustive, useful and clear in its classes. The distinction is based on objective criteria to avoid any confusion. It seems to be very simple for practical application as there are few subclasses. The observers reported no difficulty in using this classification system. This study conducted here tests the reliability of the use of this index, whether it can effectively communicate the findings to other colleagues, whether it creates confusion among different clinicians regarding difference in opinions in diagnosis. As the results of this study show that there was almost perfect agreement amongst the observers, it can be concluded that this proposed classification system by Sawai satisfies majority of the criteria, which are considered essential for a good classification system. This system can be used for studying dentitions from study casts and photographs as well.

The authors want to highlight that there were no observations of type Ⅳ subclass category in the present study. Hence, it is emphasized that this subclass cannot be documented using photographs or study models as one cannot identify an open pulp chamber in a photograph or study cast. However, this drawback can be defeated if this classification is used in clinical study as it is easy to identify an exposed pulp chamber.

To conclude, the Sawai's classification system is simple and practical to use in daily dental practice. The results of the study show that this classification is sensitive and reliable. The authors' recommend further clinical studies to assess the validity of this proposed classification system.

COMMENTS

Background

The authors, as dentists, always diagnose and monitor any particular oral disease. They use various indices to determine the severity and progression of a disease. For this, the authors use classifications or indices which are universally applied. Currently there is no ideal index for classification of tooth abrasion. A simple classification was proposed in 2014. This study evaluates the reliability of this index for use in practice.

Research frontiers

The currently available indices for tooth abrasion are time consuming. There is no uniformity regarding their grading. Hence there is an absolute need for a classification which is reliable for use in practice.

Innovations and breakthroughs

The available classifications for tooth abrasion lack uniformity and are either qualitative or quantitative in nature. This study proves that the classification used was easy to understand as dentistry students classify the tooth abrasions effectively. The classification is able to identify the position of the abrasion defect on the tooth surface and grade the severity as well.

Applications

The classification is reliable and can be used in daily dental practice.

Peer-review

The manuscript is interesting and with clinical relevance. It requires minor improvement in methodology. However, the conclusion that it can be used to classify cervical abrasions reliably is very important in dental clinics. Yet, it is important that the limitations regarding exposed pulp chamber are established.

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ORIGINAL ARTICLE

Observational Study

Effect of *Helicobacter pylori* eradication on elder cases: Observational study in community-based medicine

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Abstract

AIM

To examine the effect of *Helicobacter pylori* (*H. pylori*) eradication therapy on the extra-gastrointestinal factors in elderly patients by a before-after observational study in community medicine.

METHODS

Medical records (1 May 2013-31 January 2014) of 130 patients who underwent *H. pylori* eradication therapy with 2-year after-eradication observation in our institute were reviewed. Data on sex; age; body weight; body mass index (BMI); mean corpuscular volume (MCV); total protein; low-density lipoprotein cholesterol, triglyceride, haemoglobin A1c and haemoglobin levels and gastric hyperplastic polyps (GHPs) at eradication was extracted. Two-year after-eradication change in data was analysed by paired-sample *t*-test; relationship between GHPs and subclinical iron deficiency anaemia (IDA) improvement was evaluated.

RESULTS

The mean patient age (median, interquartile range) at eradication was 69.6 (71.5, 64-77) years. Paired-sample *t*-tests showed that body weight, BMI and MCV increased by 0.52 kg (P = 0.018), 0.25 kg/m^2 (P = 0.006) and 0.83 fL (P < 0.001), respectively. The nonparametric Mann-Whitney test showed no significant difference in the change rate of MCV after eradication between the groups with and without GHPs (P = 0.892).

CONCLUSION

H. pylori eradication therapy prevented weight loss and subclinical IDA in elderly individuals. GHPs were not associated with subclinical IDA.

Key words: *Helicobacter pylori*; Iron deficiency anaemia; Body weight; Elderly; Polyp

Core tip: The effect of *Helicobacter pylori* (*H. pylori*) eradication therapy on the extra-gastrointestinal factors in elderly patients was focused in this study. *H. pylori* eradication therapy prevented weight loss and subclinical iron deficiency anaemia (IDA) in elderly individuals. Gastric hyperplastic polyps were not associated with subclinical IDA. The results obtained in this study will help physician to treat elderly patients in community-based medicine.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection affects many extra-gastrointestinal symptoms and diseases, including iron deficiency anaemia (IDA), obesity, diabetes mellitus and hyperlipidemia[1,2]. Although major population surveys and meta-analysis have revealed an increased risk for IDA in addition to a strong evidence for the efficacy of *H. pylori* eradication for the treatment of unexplained IDA, the relationship between *H. pylori* infection and prevalence of other extra-gastrointestinal tract diseases is unclear. The influence of *H. pylori* pathogenicity is currently unknown, particularly in elderly individuals[1,3-6]. In addition, the underlying mechanism of *H. pylori*-related IDA is still unclear[7,8].

H. pylori eradication therapy for patients with peptic ulcer is associated with gain of body weight[9,10]. The relationship between *H. pylori* infection and overweight is unclear, even in large-scale epidemiological studies[11-14]. However, this increase might related to the recovery of peptic ulcer and chronic inflammation. On the other hand, because of previously reported inconsistent results, the cause-and-effect relationship between *H. pylori* infection and metabolic disease is also ambiguous, and there are few reports on elderly individuals[2,15-19]. Because the development of an aging society may be upcoming event in the near future, the effect of *H. pylori* eradication therapy on the extra-gastrointestinal organs in elderly individuals should be investigated.

Therefore, the purpose of this observational study was to examine the effects of *H. pylori* eradication in elderly individuals on systemic conditions including body weight, biochemical results, and manifestations of clinical or subclinical anaemia comparing data between before-eradication and 2 years after *H. pylori* eradication. We have also compared rates of IDA improvement in chronic gastritis with and without gastric hyperplastic polyp (GHP) to investigate the relationship between GHP and *H. pylori*-related IDA.

MATERIALS AND METHODS

This was an observational before-after study in which the case group included 130 individuals who were continuously treated with medications for chronic diseases, such as essential hypertension, hyperlipidemia and/or diabetes mellitus. They were all diagnosed with *H. pylori*-infected chronic gastritis by routine esophagogastroduodenoscopy (EGD) and the rapid urease test at Kashiwazaki Central Hospital between 1 May 2013 and 31 January 2014.

The patient was considered to be eligible when fulfilled the following inclusion criteria: (1) *H. pylori* eradication therapy was successful and was followed by the urea breath test; and (2) the patient had been measured/tested for body weight; body mass index (BMI); mean corpuscular volume (MCV); total protein (TP) and low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), haemoglobin (Hb) and haemoglobin A1c (HbA1c) levels at two time points: Before and 2 years after *H. pylori* eradication therapy was completed. However, we included patients with some missing measurement values and as elderly if older than 65 years old. We excluded patients with mucosal breaking lesions, such as gastric cancer or peptic ulcers, history of gastrointestinal surgery, and the other diseases might cause anemia. This study was approved by the institutional review board of Kashiwazaki Central Hospital. Written informed consent was obtained from all patients, and the study was conducted in accordance with the ethical guidance of the 1975 Declaration of Helsinki.

To identify differences in a patient between two time points, a paired-sample *t*-test was performed. When there were ⩽ 30 cases, a Wilcoxon signed test was performed. For continuous variables, two-group

Table 1 Comparison of various factors before and after *Helicobacter pylori* eradication therapy in all subjects (*n* = 130)

Variable	Subjects	Missing	Pre-eradication mean (SD)	Post-eradication mean (SD)	Mean difference	95%CI	*P* value
Body weight (kg)	124	6	57.3 (10.4)	58.2 (10.3)	0.52	0.09-0.94	0.018
BMI (kg/m^2)	121	9	23.4 (3.1)	23.7 (3.0)	0.25	0.074-0.42	0.006
Hb (g/dL)	115	15	13.8 (1.4)	13.8 (1.3)	0.018	-0.35	0.84
MCV (fL)	113	17	89.2 (4.9)	90 (4.4)	0.83	0.32-1.34	< 0.001
TP (g/dL)	90	40	7.4 (0.5)	7.5 (0.4)	0.024	-0.168	0.56
LDL-C (mg/dL)	107	23	114.3 (23.9)	116.2 (25.0)	1.20	-8.12	0.55
TG (mg/dL)	107	23	122 (70.5)	126.6 (77.1)	6.81	-22.59	0.23
HbA1c (%)	42	88	6.2 (0.81)	6.3 (0.75)	0.057	-0.305	0.45

BMI: Body mass index; Hb: Haemoglobin; MCV: Mean corpuscular volume; TP: Total protein; LDL-C: Low-density lipoprotein cholesterol; TG: Triglyceride; HbA1c: Haemoglobin A1c.

comparisons, such as Hb and MCV, were performed using the nonparametric Mann-Whitney test because assumptions of normality of the distribution were not verified. We excluded the patients with missing data in each group before analysis. The threshold for significance was $P < 0.05$. In all statistical analysis, we used EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics[20]. The results for changes in variable before and after *H. pylori* eradication are presented as the mean ± SD.

RESULTS

Patient characteristics

Between 1 May 2013 and 31 January 2014, 228 patients were diagnosed as having *H. pylori*-infected chronic gastritis by EGD and the rapid urease test were included. The patients who had been diagnosed as having gastric cancer ($n = 3$), gastric ulcer ($n = 16$), duodenal ulcer ($n = 20$) and gastro-duodenal ulcer ($n = 7$) who could not be followed up for 2 years after *H. pylori* eradication ($n = 52$), a total of 98 patients, were excluded from the initial 228 patients with *H. pylori*-infected chronic gastritis. Finally, a total of 130 patients [mean age, 69.6 years; median age, 71.5 (interquartile range, 64–77 years); 52 (40%) males] were analysed in the study. No patients showed re-infection of *H. pylori* after the eradication.

Effect of H. pylori eradication on various factors

The effect of *H. pylori* eradication therapy on various physiological factors was carefully examined comparing the value before and after the therapy in all 130 elderly patients with the interval of 2 years for each (Table 1). The body weight increased from a mean ± SD of 57.3 ± 10.4 kg before *H. pylori* eradication to 58.2 ± 10.3 kg 2 years after *H. pylori* eradication ($P = 0.018$). In addition, BMI increased from 23.4 ± 3.1 before *H. pylori* eradication to 23.7 ± 3.0 2 years after *H. pylori* eradication ($P = 0.006$). MCV increased from 89.2 ± 4.9 fL before *H. pylori* eradication to 90.0 ± 4.4 fL 2 years after *H. pylori* eradication ($P < 0.001$) whereas no significant changes were seen in the value of Hb ($P = 0.84$). The paired-sample *t*-test showed no significant differences in other measurements including TP, LDL-C, TG, and HbA1c, before and 2 years after *H. pylori* eradication (Table 1).

Subgroup analysis of factors in elderly patients

The patients older than 65 years old were considered to be elderly and the factors affected by the *H. pylori* eradication treatment have been carefully assessed by the subgroup analyses (Table 2). In the group of patients ⩾ 65 years ($n = 97$), BMI increased from 23.6 ± 3.0 before *H. pylori* eradication to 23.8 ± 3.1 2 years after *H. pylori* eradication ($P = 0.045$). MCV increased from 89.2 ± 5.3 fL before *H. pylori* eradication to 90.1 ± 4.7 fL 2 years after *H. pylori* eradication ($P = 0.0017$) whereas no significant changes were seen in the value of Hb ($P = 0.84$). There were no significant differences in other measurements in the group of patients ⩾ 65 years (Table 2).

These results suggest that the *H. pylori* eradication contribute to maintain the BMI avoiding the loss of body weight, and to recovery from subclinical IDA caused by the chronic inflammation in the stomach. In addition, even with the 2 years period of the study, no significant changes were seen in the various nutritional factors, indicating that the better digestion, absorption, after the eradication therapy.

Effect of eradication and the level of Hb

To determine the effect of eradication on anaemia, level of Hb was carefully assessed in the patients (Table 3). Although the patients with Hb levels < 12.5 g/dL before *H. pylori* eradication increased from 11.5 ± 0.86 g/dL to 12.3 ± 0.99 g/dL at 2 years after *H. pylori* eradication ($P = 0.017$), paired-sample t-tests showed no significant difference in Hb levels before and 2 years after *H. pylori* eradication in the group with Hb ⩾ 12.5 g/dL (Table 3). In addition, to examine whether the rates of IDA improvement in chronic gastritis is related to the existence of GHP, the level of improvement of Hb and MCV values before and after the eradication

Table 2 Subgroup analysis of various factors before and after *Helicobacter pylori* eradication therapy in the group of patients > 65 years (*n* = 97)

Variable	Subjects	Missing	Pre-eradication mean (SD)	Post-eradication mean (SD)	Mean difference	95%CI	*P* value
Body weight (kg)	92	5	57.1 (10.4)	57.8 (10.3)	0.41	-1.017	0.12
BMI (kg/m^2)	90	7	23.6 (3.0)	23.8 (3.1)	0.21	-0.4159	0.045
Hb (g/dL)	85	12	13.7 (1.5)	13.7 (1.3)	-0.02	-0.4	0.84
MCV (fL)	85	12	89.2 (5.3)	90.1 (4.7)	0.95	-1.17	0.0017
TP (g/dL)	66	31	7.5 (0.5)	7.5 (0.4)	0.011	-0.216	0.84
LDL-C (mg/dL)	77	20	111.9 (21.2)	114.2 (24.8)	1.25	-9.65	0.61
TG (mg/dL)	77	20	116.7 (56.2)	112.6 (44.8)	-1.68	-20.35	0.74
HbA1c (%)	30	67	6.4 (0.8)	6.4 (0.7)	0.013	-0.35	0.88

BMI: Body mass index; Hb: Haemoglobin; MCV: Mean corpuscular volume; TP: Total protein; LDL-C: Low-density lipoprotein cholesterol; TG: Triglyceride; HbA1c: Haemoglobin A1c.

Table 3 Differences in the eradication effect on the rate of increase in haemoglobin level between groups of patients with < haemoglobin 12.5 g/dL (*n* = 20) and patients with ⩾ haemoglobin 12.5 g/dL (*n* = 96)

Variable	Subjects	Missing	Pre-eradication mean (SD)	Post-eradication mean (SD)	Mean difference	95%CI	*P* value
Less than Hb 12.5 g/dL	19	1	11.5 (0.7)	12.3 (1.0)	0.85	0.22-1.48	0.017
More over Hb 12.5 g/dL	96	11	14.2 (1.1)	14.1 (1.2)	-0.15	-0.1592	0.064

Hb: Haemoglobin.

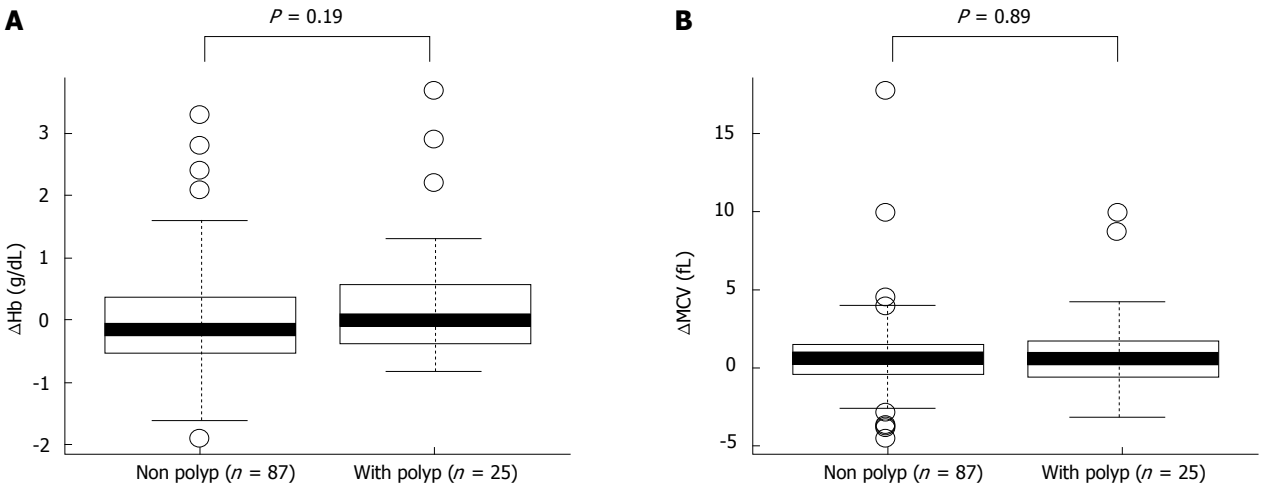

Figure 1 Comparison of haemoglobin and mean corpuscular volume levels before and after *Helicobacter pylori* eradication therapy in patients with or without gastric hyperplastic polyps. A: Change in the haemoglobin level; B: Mean corpuscular volume level. Hb: Haemoglobin; MCV: Mean corpuscular volume.

were compared (Figure 1). The nonparametric Mann-Whitney test showed no significant increase in Hb levels and MCV (P = 0.89) from before to 2 years after *H. pylori* eradication (P = 0.19) between the groups with and without GHP (Figure 1) and its size. These results indicate that the improving tendency of anaemia after *H. pylori* eradication did not correlate with the presence of GHP or its size.

DISCUSSION

Our study showed that *H. pylori* eradication therapy for elderly patients with chronic gastritis increased BMI and MCV, 2 years as a result of successful *H. pylori* eradication. The level of MCV has been considered as one of the marker of subclinical IDA and its recovery reflect the improvement of IDA[21]. Previous studies have shown similar results in patients with anaemia whose Hb significantly improved after *H. pylori* eradication[1,3-6]. There was no difference in the rate of increase in MCV (improvement in IDA) between groups with and without GHP. This finding suggests that GHP is not involved in an anaemic improvement pathway after *H. pylori* eradication.

It is known that the proportion of individuals with BMI > 30 generally increases up to the age of 60 years, and BMI tends to decrease after the age of 61 years[22]. In addition, the body weight loss in elderly individuals

is a predictive factor for death, mildly obese individuals have the lowest mortality rate[23,24]. It might be related to the recently established concept of "Frailty", a risk factor for falls, disability, hospitalization and mortality during old age. It is defined by the following criteria: Unintentional weight loss, self-reported exhaustion, weakness (grip strength), slow walking speed and low physical activity[25] and energy and protein support is recommended to treat the condition[26]. Interestingly, in our study, we found that elderly patients gained weight after *H. pylori* eradication. This result was inconsistent with the general tendency towards body weight loss in the elderly population and suggested that the effect of *H. pylori* eradication on preventing body weight loss or increase. The mechanisms might include, improvement of gastro-duodenal inflammation, ulcerative lesions, *etc*., as well as decrease of serum level of leptin which plays a crucial role to regulate food intake and energy expenditure[11,27]. Thus, we infer that *H. pylori* eradication therapy for elderly patients with *H. pylori*-infected chronic gastritis may be an effective therapy for prevention of weight loss in elderly individuals.

Our results are consistent with those of previous studies showing improvement of anaemia after *H. pylori* eradication therapy in elderly individuals[1,3-6]. Our study also showed that MCV increased after *H. pylori* eradication in the total study population as well as in the elderly patient group. However, presence of GHP was not related to the increase in the MCV rate. An important finding from previous study is that 80% of GHP disappeared after *H. pylori* eradication therapy within an average of 7.1 mo[28]. A recent report suggested that *H. pylori*-related IDA was associated with several factors in patients with GHP and nodular gastritis[29]. Bleeding from GHP is assumed to be the cause of *H. pylori*-related IDA. However, a previous study showed that even faecal occult blood-negative patients may be anaemic[30]. In addition, the mechanism might not be applicable to nodular gastritis. A recent study suggested that the cause of anaemia in patients with GHP is not bleeding from GHP but rather a decrease in iron absorption caused by a low-acid state[26]. Therefore, our results provide some support for the hypothesis that the improvement of *H. pylori*-related IDA is caused by an underlying mechanism other than GHP deletion.

One plausible reason for the finding of no significant changes in TP, TG, LDL-C and HbA1c levels is the presumed administration of statins and/or antidiabetic drugs to the patients. A previous report showed that serum total cholesterol levels did not change after *H. pylori* eradication[11]. Therefore, our results may be consistent with these previous findings.

A limitation of our study, however, is that although previous studies have shown that diabetes was exacerbated by *H. pylori* infection[17-19], our findings suggest no exacerbation or improvement of diabetes by eradication was because of strict management by a diabetologist in our hospital. In addition, the power of this study was limited because of the small number of participants and patients with subclinical IDA, of the single-centre analysis and of the retrospective-observational study design. Therefore, future larger, ad hoc, and better designed prospective studies are essential to confirm the effect of *H. pylori* eradication on systemic conditions by monitoring symptoms, medical history, and laboratory exams comparing with cases failed for the eradication.

In conclusion, our findings suggest that an increase in MCV is associated with body weight gain and improvement of subclinical IDA after *H. pylori* eradication in elderly patients with chronic gastritis. The tendency for subclinical IDA to improve after *H. pylori* eradication did not correlate with the presence of GHP. In addition, even with the 2 years period of the study, no significant changes were seen in the various nutritional factors, indicating that the better digestion, absorption, after the eradication therapy. For the future perspective, as the development of an aging society may be upcoming event in the near future, *H. pylori* eradication therapy may be a useful approach for preventing weight loss and frailty in elderly individuals to keep their quality of life and health.

ARTICLE HIGHLIGHTS

Research background

The relationship between *Helicobacter pylori* (*H. pylori*) infection and various extra-gastrointestinal symptoms, including obesity, diabetes mellitus and hyperlipidemia have been reported.

Research motivation

Although major population surveys and meta-analysis have suggested an increased risk for iron deficiency anaemia (IDA), however the relationship between *H. pylori* infection/its eradication on IDA and other extra-gastrointestinal tract diseases has not been clarified, especially in elderly patients.

Research objectives

This study was aimed to examine the effect of *H. pylori* eradication therapy on the extra-gastrointestinal factors in elderly patients by a before-after observational study in community medicine.

Research methods

Medical records (1 May 2013-31 January 2014) of 130 patients who underwent *H. pylori* eradication therapy with 2-year after-eradication observation in our institute were reviewed. Data on sex; age; body weight; body mass index (BMI); mean corpuscular volume (MCV); total protein; low-density lipoprotein cholesterol, triglyceride, haemoglobin A1c and haemoglobin levels and gastric hyperplastic polyps (GHPs) at eradication was extracted. Two-year after-eradication change in data was analysed by paired-sample *t*-test; relationship between GHPs and subclinical IDA improvement was evaluated.

Research results

The mean patient age (median, interquartile range) at eradication was 69.6 (71.5, 64-77) years. Paired-sample *t*-tests showed that body weight, BMI and MCV increased by 0.52 kg (P = 0.018), 0.25 kg/m^2 (P = 0.006) and 0.83 fL (P < 0.001), respectively. The nonparametric Mann-Whitney test showed no significant difference in the change rate of MCV after eradication between the groups with and without GHPs (P = 0.892).

Research conclusions

H. pylori eradication therapy prevented weight loss and subclinical IDA in elderly individuals, therefore, the eradication should be considered even for

those elder patients.

Research perspectives

For the future perspective, as the development of an aging society may be upcoming event in the near future, *H. pylori* eradication therapy may be a useful approach for preventing weight loss and frailty in elderly individuals to keep their quality of life and health.

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CASE REPORT

Surgical resection of rare internal jugular vein aneurysm in neurofibromatosis type 1

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Author contributions: Delvecchio K, Moghul F and Patel B examined patient and collected clinical data; Moghul F and Patel B performed surgical resection and follow up; Delvecchio K and Moghul F wrote the paper; Patel B and Seman S edited the manuscript and had final approval.

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Informed consent statement: Informed written consent was obtained from the patient prior to all procedures described in the report as well as for the use of the patient's clinical information and images for published scientific works.

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Abstract

Neurofibromatosis type 1 is a congenital condition affecting neurons and connective tissue integrity including vasculature. On extremely rare occasions these patients present with venous aneurysms affecting the internal jugular vein. If they become large enough there presents a risk of rupture, thrombosis, embolization or compression of adjacent structures. In these circumstances, or when the patient becomes symptomatic, surgical exploration is warranted. We present a case of one of the largest aneurysms in the literature and one of only five associated with Neurofibromatosis type 1. A 63-year-old female who initially presented for a Hinchey Ⅲ diverticulitis requiring laparotomy developed an incidentally discovered left neck swelling prior to discharge. After nonspecific clinical exam findings, imaging identified a thrombosed internal jugular vein aneurysm. Due to the risks associated with the particularly large size of our patient's aneurysm, our patient underwent surgical exploration with ligation and excision. Although several techniques have been reported, for similar presentations, we recommend this technique.

Key words: Internal jugular; Venous aneurysm; Ligation; Neurofibromatosis 1; Excision; Resection

Core tip: Neurofibromatosis type 1 is a congenital condition occasionally affecting vascular connective tissue integrity. On extremely rare occasions these patients present with internal jugular venous aneurysms. We

present a case of the successful ligation and excision of one of the largest internal jugular vein aneurysms in the literature and one of only five associated with Neurofibromatosis type 1.

Delvecchio K, Moghul F, Patel B, Seman S. Surgical resection of rare internal jugular vein aneurysm in neurofibromatosis type 1. *World J Clin Cases* 2017; 5(12): 419-422 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i12/419.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i12.419

INTRODUCTION

Initially described by Gruber[1] in 1875, internal jugular (IJ) aneurysms are rare entities with under 400 reported in the last 100 years in the literature. As described by Lubianca-Neto *et al*[2] these lesions have historically been described as "congenital venous cyst, venous pseudoaneurysm, venous ectasia, venous aneurysm, venous cyst, venoma, and internal jugular phlebectasia" in the literature, with an average age of under 10 and over 60% under age 40[3,4]. They most commonly occur on the right side, however may be bilateral in as many as 10% of cases[5,6]. These aneurysms classically present as unilateral, asymptomatic, soft, compressible neck swellings that enlarge with Valsalva[1-3]. Due to the relationship of the IJ abutting the vagus nerve within the carotid sheath, patients may complain of hoarseness, dysphagia or foreign body sensation[1,5,7]. Moreover, the absence of bruit or pulsation on physical exam excludes a more ominous arterial pathology[1,8].

While the underlying physiology that makes a particular patient susceptible to aneurysm formation is largely unknown, several inciting factors have been reported in the literature. These include trauma from central venous catheterization, positive-pressure ventilation, inflammation, distal obstruction from a mass, or unknown idiopathic causes[2,7,9]. Additionally, pathological analyses of resected aneurysms have described congenital thinning of the elastic and muscular layers of the venous wall, and/or elastin dysplasia[10,11]. Not surprisingly, disorders of connective tissue, including Ehlers-Danlos and Neurofibromatosis type 1 (NF1), have been linked to these anomalies[4,12-14].

NF1 aka von Recklinghausen's disease is an autosomal dominant mutation of chromosome 17 occurring in 1 in 3000 people that alters the neurofibromin protein, affecting the structural integrity of connective tissues and nerves[12,13]. Typical presentations include neurofibromas, café au lait macules, Lisch hamartomas, meningiomas, and gliomas[13,14]. Rarer manifestations involve the vasculature which can be present in up to 6.4% of patients, however it primarily involves the arterial system[12,15]. We present a case of the successful ligation and excision of one of the largest IJ vein aneurysms in the literature and one of only five associated with NF1.

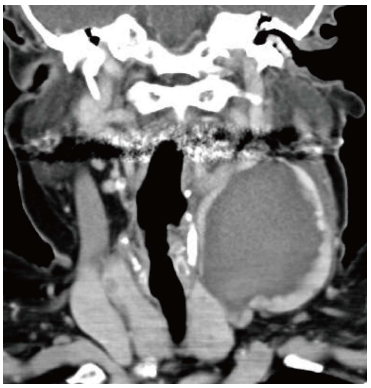

Figure 1 Coronal computed tomography of left internal jugular vein aneurysm.

CASE REPORT

A 63-year-old Caucasian female with a medical history significant for Neurofibromatosis presented to the emergency room with bilateral lower quadrant abdominal pain, diarrhea, emesis and complaints of fevers and chills for one day. She was tachycardic and peritoneal on examination and thus taken to the operating room where she underwent sigmoid resection with end colostomy and Hartmann's pouch for Hinchey Ⅲ diverticulitis. Postoperatively the patient remained intubated and was admitted to the ICU and had a left subclavian central venous catheter placed for vasopressor support. After a series of setbacks, the patient began to improve significantly around postoperative day (POD) 11 and her subclavian line was able to be removed. By POD 15 the patient was ready for discharge to rehab.

Upon preparing for departure the patient noticed in the mirror a bulge in her left neck that she did not previously feel. The nursing staff and subsequently physicians were notified. Upon examination there was no noticeable mass as the patient had significant submental ptosis. A computed tomography (CT) scan of the neck was performed which showed a 5.8 cm × 6.9 cm × 5.4 cm internal jugular collection with anterior displacement of the sternocleidomastoid (SCM) (Figures 1 and 2). The vascular surgeon was notified and a triplex ultrasound was performed showing a 6.9 cm × 3.8 cm × 6.5 cm internal jugular thrombus with minimal superior flow and a patent subclavian (Figure 3).

On POD 16 the patient was taken to the operating room where she underwent evacuation, resection and ligation of the internal jugular aneurysm *via* an anterior SCM incision. Small internal branches were ligated and the anterior vein wall was sutured closed. There was an estimated blood loss of 1 liter during dissection due to avulsion of many of these internal branches. The skin was closed and a Jackson-Pratt (JP) drain was left subcutaneously. Postoperatively the JP was removed on day 1 due to minimal output and the patient was able to be discharged home on day 2.

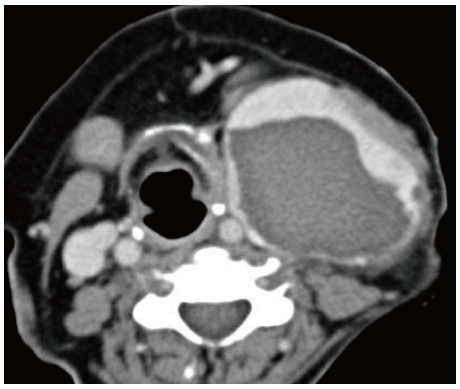

Figure 2 Transverse computed tomography of left internal jugular vein aneurysm.

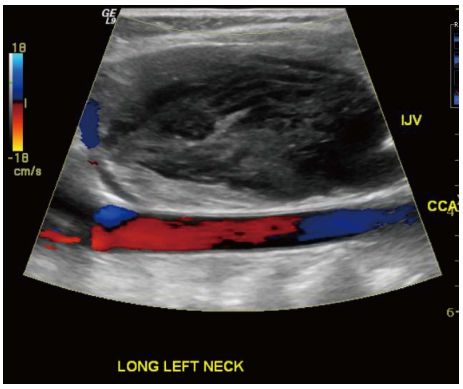

Figure 3 Color flow doppler ultrasound image depicting patent left common carotid artery and thrombosed left internal jugular vein aneurysm.

Table 1 Characteristics of Neurofibromatosis type 1-associated internal jugular aneurysms in the literature

Ref.	Age/sex	Side	Size (cm)	Treatment	Thrombosed	Confirmed NF1 in wall
Nopajaroonsri and Lurie[14] (1996)	62 M	Left	10 × 5 × 4.5	Resection	Yes	Yes
Oderich *et al*[13] (2007)	73 M	Right	"Giant"	Resection	Yes	
Belcastro *et al*[15] (2011)	60 F	Left	12 × 12 × 10	Resection	Yes	Yes
Hiraki *et al*[12] (2014)	60 M	Left	5.5 × 5 × 2	Resection	Yes	Yes
The present case	63 F	Left	6.9 × 5.8 × 5.4	Resection	Yes	

M: Male; F: Female; NF1: Neurofibromatosis type 1.

DISCUSSION

Limitations to our workup include not submitting the aneurysmal wall for pathological analysis as 3 of the 4 described aneurysms associated with NF1 in the literature describe histopathological invasion of NF1 into the wall[12,14,15]. While not necessary for the diagnosis, it could have helped substantiate a more definitive pathological explanation. Additionally, several authors have recommended that the diagnostic workup include bilateral triplex ultrasound performed with Valsalva[4-6]. The importance of a size increase with Valsalva during examinations is underscored by the fact that the majority of differential diagnoses can be ruled out if absent, leaving phlebectasias, laryngoceles and superior mediastinal cyst[4]. The most common of these, laryngocele, can be ruled out with laryngoscopy, whereas mediastinal cysts can be ruled out with CT scan[5]. Although our patient's diagnosis was easily identified with CT and confirmed with triplex ultrasound, it was not performed with these particular suggestions in mind.

Although clinical exam can provide a significant amount of information, because of the low overall rate of complications there is often adequate time for definitive imaging. As mentioned previously, triplex ultrasound is the current standard for diagnostic accuracy as it will allow for characterization of the aneurysmal size as well as visualization of directional blood flow and thrombosis[2,4,5]. Additionally, Passariello *et al*[16], described four cases in children that were successfully characterized with endovascular digital subtraction contrast fluoroscopy which has the additional benefit of simultaneous diagnosis and intervention[17].

As described above, a commonly cited etiology of IJ aneurysms is traumatic central venous catheterization[7]. A limitation with our case was the prolonged duration with which her left subclavian line was in place, possibly leading to thrombosis and propagation. It is difficult to definitively determine if the subclavian line was the inciting event, however it is likely it participated in a genetically susceptible patient.

IJ aneurysms have rarely been reported on and only a handful have been described in association with NF1 (Table 1)[12-15]. These lesions typically present much larger than other cases and ours, at 6.9 cm × 5.8 cm × 5.4 cm, is one of the largest described in the literature. Each of these aneurysms were surgically resected and each had significant blood loss[12-15].

With regard to management, because IJ aneurysms are considered to be self-limiting, operative intervention is usually reserved for cosmetic or symptomatic reasons[2,5,10,18]. Although extremely rare, if there is significant concern for thrombosis, embolization or impending rupture, resection is justified[10]. Various approaches have been described which have been largely based on size and location, including anterior SCM, transverse cervical and median sternotomy incisions[4,5,15]. Additionally Chua *et al*[17], describe a combined endovascular balloon ligation and open resection, allowing for a smaller incision. Regardless of the approach, it is important preoperatively to confirm contralateral patency for cerebral edema prevention[2] as Hu *et al*[8], reported 2 cases of unilateral ligation of bilateral lesions resulting in 3

d of cerebral swelling. While many IJ vein aneurysms have reportedly been followed successfully without intervention for up to 15 years, no studies have been performed that compare long-term outcomes of any kind[6]. This leads to the suggestion of future randomized trials featuring long-term outcomes of conservative management *vs* various surgical procedures.

COMMENTS

Case characteristics

A 63-year-old woman with neurofibromatisis type 1 who developed an incidentally discovered internal jugular vein aneurysm that was surgically resected.

Clinical diagnosis

Compressible left-sided neck swelling without dysphagia or respiratory compromise.

Differential diagnosis

Differential diagnoses include phlebectasias, laryngoceles, superior mediastinal cyst, thyroglossal duct cyst, cystic hygroma, branchial cleft cyst, pharyngocele, dermoid cyst, thyroid mass, arteriovenous malformation, carotid body tumor and squamous cell carcinoma of the neck.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

Computed tomography scan showed a 5.8 cm × 6.9 cm × 5.4 cm internal jugular collection with anterior displacement of the sternocleidomastoid. A triplex ultrasound showed a 6.9 cm × 3.8 cm × 6.5 cm internal jugular thrombus with minimal superior flow and a patent subclavian.

Treatment

Surgical evacuation, resection and ligation of the aneurysm.

Related reports

Internal jugular venous aneurysms have historically gone by several names in the literature and despite very few resulting in significant morbidity with expectant management alone, they are frequently surgically resected.

Term explanation

Triplex ultrasound is an imaging method that uses color to highlight direction of vascular flow. It is the recommended diagnostic method to characterize these lesions.

Experiences and lessons

Patients with neurofibromatosis type 1 are particularly susceptible to internal jugular vein aneurysms due to vascular wall abnormalities, which should be noted when inciting etiological events occur such as central venous catheterization.

Peer-review

The information and brief literature review provided was sufficient.

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CASE REPORT

Human herpesvirus-8 positive iatrogenic Kaposi's sarcoma in the setting of refractory ulcerative colitis

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Abstract

Although Kaposi sarcoma (KS) has been more traditionally considered an AIDS-defining illness, it may also be seen in individuals on immunosuppresive therapy. We report a case of a patient who presented to the hospital in the setting of increasingly refractory ulcerative colitis. Computed tomography scan of the abdomen was consistent with sigmoid diverticulititis and blood cultures were positive for Klebsiella. After a course of antibiotics with resolution of infection, a colonoscopy was performed to evaluate his diverticulitis and incidentally revealed a new rectal tumor. Immunohistochemistry showed the tumor was consistent with KS, with cells staining strongly positive for human herpesvirus-8. This case not only illustrates a rare case of KS found in an HIV-negative individual, but it also highlights the importance of considering an alternative diagnosis in a patient refractory to medical treatment. We discuss the management and care of an ulcerative colitis patient diagnosed with KS on immunosuppressive therapy.

Key words: Kaposi sarcoma; Colorectal cancer; Ulcerative colitis; Inflammatory bowel disease; HIV/AIDS; Human herpesvirus-8

Core tip: Kaposi sarcoma (KS) is associated with human herpes 8 virus infection and is typically an acquired immune deficiency syndrome defining illness. However, KS may also be seen in patients who are on long-term immunosuppression. Review of the literature suggests that isolated gastrointestinal KS is a very rare complication, as there are less than 20 reported cases in the English language literature in ulcerative colitis HIV negative

host. Our findings contribute to a small body of literature illustrating the manifestation of primary gastrointestinal KS without skin manifestations in a patient with refractory colitis to medical management.

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INTRODUCTION

Kaposi sarcoma (KS) is a vascular neoplasm caused by human herpesvirus-8 (HHV-8) infection in an immunocompromised host. There are four settings in which KS occurs: The classic form (in elderly men of Mediterranean or Eastern European background), the endemic form (in individuals of African background), the HIV-associated form, and the iatrogenic form[1]. The latter form is most commonly seen after solid organ transplantation. There are, however, several case reports of colonic KS associated with ulcerative colitis, typically in refractory cases requiring either intermittent or continuous corticosteroids. Interestingly, no association has been noted between the development of KS and duration of ulcerative colitis (UC) disease activity[2]. The relationship between KS and corticosteroid dose or duration of therapy has not been deeply explored, though there have been case-control studies that suggest oral corticosteroid use is independently associated with increased risk of classical KS[3]. Clinical manifestations may include characteristic skin lesions (not present in this case) or intraluminal vascular-appearing colonic tumors. The lack of skin lesions in primary gastrointestinal KS makes the diagnosis challenging. We report a case of a HIV-negative patient with refractory ulcerative colitis who was diagnosed with KS on histopathological examination of rectal tissue.

CASE REPORT

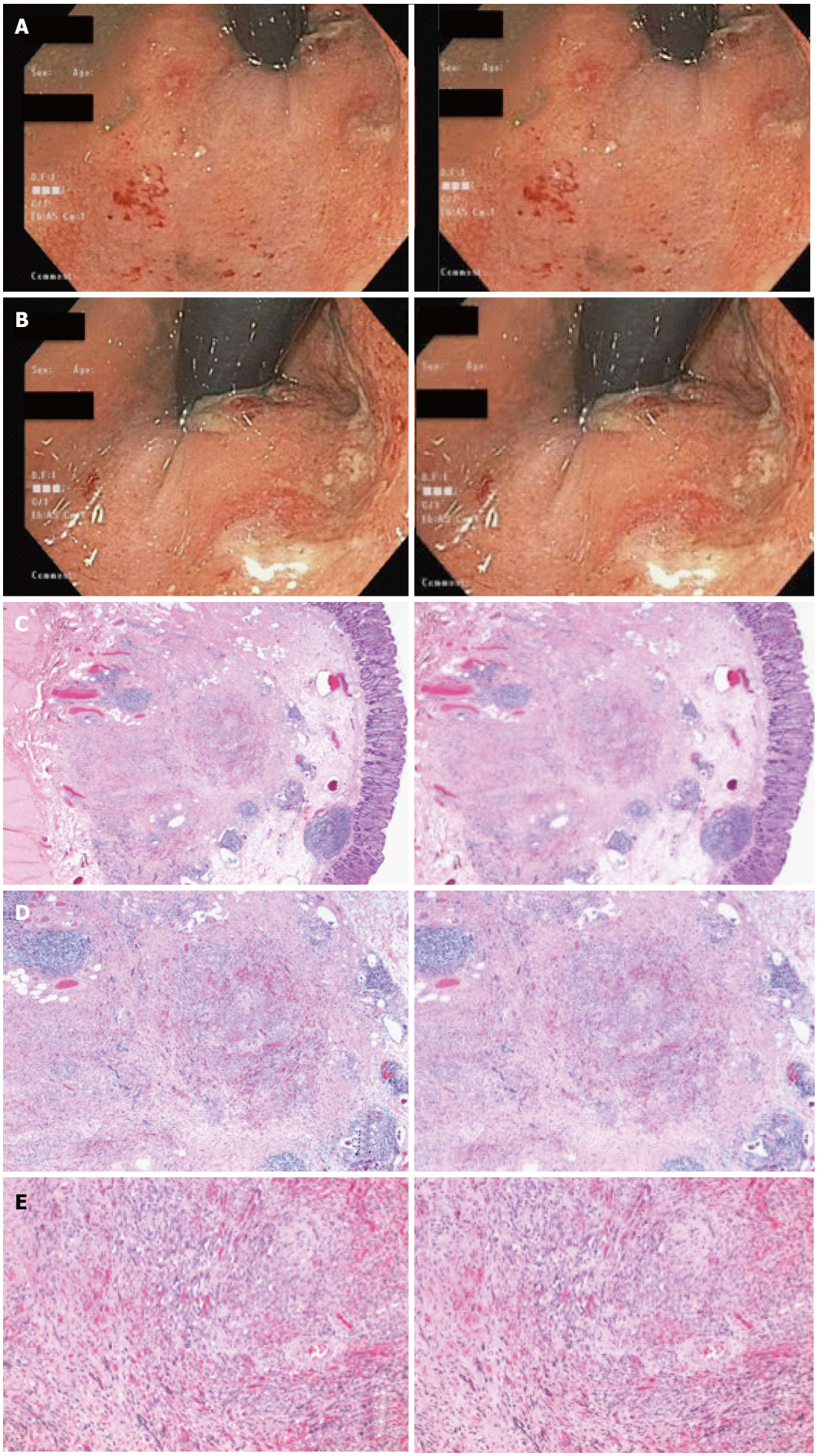
A 48-year-old man with a long-standing history of left-sided UC for 25 years presented to the hospital with fever, nausea, diarrhea and hematochezia for four days. His UC had become increasingly refractory the year prior to presentation with numerous flares that were managed with steroids. Attempts to taper and withdraw steroids had led to multiple relapses. He was started on azathioprine just eight months prior to his presentation and the remainder of his medication at the time of admission included prednisone and pantoprazole.

His exam at the time of presentation was largely unremarkable with a soft, non-tender abdomen without rebound or guarding and no evidence of skin rashes. Vital signs included a temperature of 98.6 °F, a heart rate of 62 bpm, and a blood pressure of 143/84 mmHg. Labs were notable for a hemoglobin of 12.3 g/dL (13.5-16), WBC of 10.1 × 10^9/L (3.5-11) and a negative HIV antibody. A CT scan of the abdomen showed sigmoid wall-thickening, luminal narrowing and surrounding inflammatory stranding with a small fluid collection. He was diagnosed with sigmoid diverticulitis complicated by a 3 cm abscess that was felt to not be amenable to drainage. Blood cultures were positive for Klebsiella and he was treated with a fourteen-day course of antibiotics. A colonoscopy was performed following resolution of acute diverticulitis and revealed a tumor in the rectum (Figure 1A and B). Biopsies of the distal colon revealed focal active colitis and proximal biopsies of the left colon demonstrated crypt architectural irregularities and paneth cell metaplasia consistent with quiescent colitis. Histologic sections of the rectal tumor demonstrated a cytologically bland spindle cell proliferation interspersed by irregular vascular spaces containing extravasated erythrocytes (Figures 1C-E). By immunohistochemistry, the lesional cells were strongly positive for HHV-8 (Figures 1F and G) and consistent with KS. Esophagogastroduodenoscopy and capsule endoscopy demonstrated that tumor involvement was limited to the rectum. In consultation with a sarcoma specialist, the treatment plan involved an attempt at immune reconstitution by withdrawal of steroids. Over the period of a year, attempts to taper the patient off of steroids by introducing alternative agents (including aloe vera, probiotics, phostatidylcholine and Epigallocatechin-3-gallate) were unsuccessful and led to repeated relapses. Surveillance colonoscopies completed four and seven months following diagnosis revealed persistent Kaposi rectal tumor. The patient went on to have a definitive laparoscopic assisted subtotal colectomy with end ileostomy and since has done well.

DISCUSSION

KS is a rare diagnosis and is typically diagnosed when the classic skin manifestations are present. Isolated gastrointestinal KS may occur in patients with ulcerative colitis as a result of the dysregulated immune response seen in IBD or in combination with medications causing immune suppression. Symptoms and signs of gastrointestinal KS may include diarrhea, bleeding, obstruction, and rarely perforation. A misdiagnosis of refractory ulcerative colitis may occur in part because the initial presentation may mimic a IBD flare with diarrhea and rectal bleeding and may be severe to the point requiring blood transfusions[4]. The reason KS lesions are predisposed to bleeding is that they are angioproliferative tumors. Typically, KS lesions in the intestinal tract tend to localize more to the upper intestinal tract and are less frequently encountered in the large bowel[5].

This is one of the few reported cases in the English language literature of large bowel KS associated with ulcerative colitis in an HIV-negative host with positive HHV-8 immunohistochemistry. Infection with HHV-8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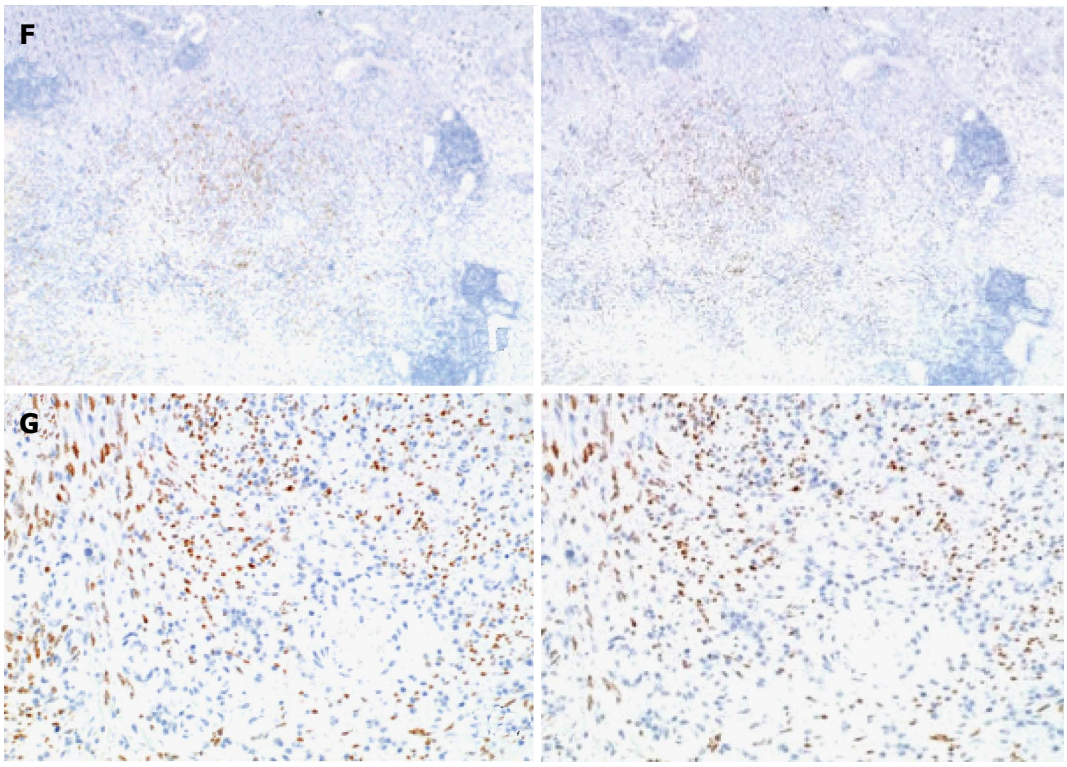

Figure 1 Colonoscopy, histologic and immunohistochemistry. A: A colonoscopy was performed following resolution of acute diverticulitis, revealing a tumor in the rectum. Biopsies of the colon revealed distal focal active colitis as well as more proximal crypt architectural irregularities and paneth cell metaplasia consistent with quiescent colitis; B: A colonoscopy was performed following resolution of acute diverticulitis, revealing a tumor in the rectum. Biopsies of the colon revealed distal focal active colitis as well as more proximal crypt architectural irregularities and paneth cell metaplasia consistent with quiescent colitis; C: Histologic sections of the rectal tumor demonstrated a cytologically bland spindle cell proliferation interspersed by irregular vascular spaces containing extravasated erythrocytes (2 ×); D: Histologic sections of the rectal tumor demonstrated a cytologically bland spindle cell proliferation interspersed by irregular vascular spaces containing extravasated erythrocytes (4 ×); E: Histologic sections of the rectal tumor demonstrated a cytologically bland spindle cell proliferation interspersed by irregular vascular spaces containing extravasated erythrocytes (10 ×); F: By immunohistochemistry, the lesional cells were strongly positive for human herpesvirus-8 and consistent with Kaposi's sarcoma (4 ×); G: By immunohistochemistry, the lesional cells were strongly positive for human herpesvirus-8 and consistent with Kaposi's sarcoma (10 ×).

is a known precedent to the development of all types of KS and has been found in over 95% of cases[5]. The literature shows that only a small proportion of HHV-8 infected people develop Kaposi Sarcoma, suggesting that additional iatrogenic causes such as immunosuppressive drugs could cause viral reactivation, and contribute to the development of KS[6].

Corticosteroid use was first implemented in the 1950's for the management of Ulcerative colitis and has played a pivotal role in decreasing mortality[7]. However, over the years evidence has demonstrated poor outcomes for patients who remain on longterm steroids, notably an increased risk for infections and mortality[8]. In the first population-based field study of classical Kaposi sarcoma, use of oral corticosteroids showed a increased risk for the development of KS (OR = 2.34, 95%CI: 1.23-4.45)[3]. KS has also been reported to be higher in illnesses that are commonly treated with corticosteroids including asthma and rheumatic diseases[9,10]. Studies have shown that glucocorticoids can induce KS and drive progression in multiple different clinical settings through interactions with the gene Transforming growth factor-β (TGF-β). This gene has several effects, one of which is inhibition of cell growth. While glucocorticoids have no effect on the actual transcription of TGF-β, the medication does decrease activation of the TGF-β gene by downregulating plasminogen activator and plasminogen activator receptor, which are known to drive the TGF-β activation pathway[13]. Thus, glucocorticoids reduce levels of plasmin, which prevents activation of TGF-β, and in turn decreases its inhibitory effects on KS cells[11].

Diagnosis of KS in the absence of characteristic skin lesions can be difficult as colonic KS development starts in the submucosa and standard biopsies may not prove diagnostic. Therefore if there is a high suspicion, "bite on bite" biopsies should be taken with large forceps, which may improve the diagnostic yield[6]. When the mucosa is involved, tumors may appear similar to pseudopolyps. Cross sectional imaging may only demonstrate colonic wall thickening. Serum PCR for HHV-8 is an available test that may be useful in the diagnosis and in guiding decision for early surgical management[12]. Treatment consists of immune reconstitution and should be pursued to prevent systemic dissemination of disease[5]. Withdrawal of immunosuppressive agents, which often requires surgical colonic resection, can lead to regression or cure of KS lesions. Lastly, involvement of a multidisciplinary treatment team is vital to coordination of care and ensuring resolution of the disease.

COMMENTS

Case characteristics
Patient's symptoms included fever, nausea, diarrhea, and hematochezia.

Clinical diagnosis
Patient was found to have a rectal tumor consistent with Kaposi sarcoma (KS) after having had surveillance colonoscopies completeded.

Differential diagnosis
Ulcerative colitis flare, vascular transformation of lymph nodes, CMV colitis, infectious colitis.

Laboratory diagnosis
Labs were notable for a hemoglobin of 12.3 g/dL (13.5-16), WBC of 10.1 × 10^9/L (3.5-11) and a negative HIV antibody.

Imaging diagnosis
Esophagogastroduodenoscopy and capsule endoscopy demonstrated that tumor involvement was limited to the rectum.

Pathological diagnosis
Histologic sections of the rectal tumor demonstrated a cytologically bland spindle cell proliferation interspersed by irregular vascular spaces containing extravasated erythrocytes, which on immunohistochemistry were positive for human herpesvirus-8 and consistent with KS.

Treatment
The patient underwent multiple failed attempts to withdraw his regimen of oral corticosteroids, and ultimately received a laparoscopic assisted subtotal colectomy with end ileostomy and since has done well.

Term explanation
Refractory: Resistant to a process or stimulus, in the context of medicine this term often refers to being resistant to treatment. Immunosuppression: Reduction of the activation or efficacy of the immune system

Experiences and lessons
This particular patient's case highlights the importance in considering the diagnosis of KS in the setting of ulcerative colitis patients, as failure to do so delay treatment.

Peer-review
This patient case illustrates the manifestation of primary gastrointestinal KS in a patient with refractory colitis to medical management.

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CASE REPORT

Sickle-cell and alpha-thalassemia traits resulting in non-atherosclerotic myocardial infarction: Beyond coincidence?

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Author contributions: Nguyen LS wrote the manuscript and performed literature research and reviewing; Redheuil A provided with image interpretation and critical reviewing; Mangin O contributed to the edition and reviewing; Salem JE supervised the work and provided critical reviewing and editing.

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Abstract

Alpha-thalassemia trait and sickle trait are not commonly considered risk factors of ischemic heart disease. We report the case of a non-atherosclerotic silent myocardial infarction in a 46-year-old woman, carrier of the alpha-thalassemia trait (homozygous deletion of locus -3.7) combined with sickle cell trait. While the patient was included as healthy volunteer for a metabolic study, we performed cardiac magnetic resonance imagery showing a left ventricle apicolateral myocardial infarction. Coronary computed tomography angiography showed normal coronary arteries with a coronary calcium score of 0. The patient was treated with low-dose aspirin in secondary prevention afterwards. This case allows us to discuss cardiovascular risk among patients presenting with both alpha-thalassemia trait and sickle cell trait and the indication of cardiac imagery in such patients even when considered as low-cardiovascular risk.

Key words: Alpha-thalassemia trait; Sickle-cell trait; Non-atherosclerotic myocardial infarction; Cardiovascular risk

factor; Coronary computed tomography angiography

Core tip: Alpha-thalassemia trait and sickle trait are not considered risk factors of ischemic cardiopathy. We reported the case of a non-atherosclerotic silent myocardial infarction in a 46-year-old woman, carrier of the alpha-thalassemia trait combined with sickle cell trait. While the patient was included as healthy volunteer for a metabolic study, we performed cardiac magnetic resonance imagery showing a left ventricle apicolateral myocardial infarction. Coronary computed tomography angiography showed normal coronary arteries with a null calcium score. The patient was treated with low-dose aspirin in secondary prevention afterwards. This case allows us to discuss cardiovascular risk among patients presenting with alpha-thalassemia trait and sickle cell trait.

Nguyen LS, Redheuil A, Mangin O, Salem JE. Sickle-cell and alpha-thalassemia traits resulting in non-atherosclerotic myocardial infarction: Beyond coincidence? *World J Clin Cases* 2017; 5(12): 428-431 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i12/428.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i12.428

INTRODUCTION

Sickle-cell trait and alpha-thalassemia trait are associated in 10% of sub-Saharan population. Both are asymptomatic. The cardiovascular risk associated with both traits is unknown. We here report the case of a 46-year-old female patient, asymptomatic, who was diagnosed with both traits and a silent non-atherosclerotic myocardial infarction. This case raises the question of performing cardiac imagery in such patients and assessing their cardiovascular risk.

CASE REPORT

We report the case of a 46-year-old female patient of Erythrean origin who was included as healthy volunteer in a French observational trial on lipid metabolism during which blood analyses and cardiac magnetic resonance imaging (cMRI) were performed. Presence of myocardial silent infarction was measured using cMRI by evaluating presence and quantification of late gadolinium enhancement (LGE). In addition to LGE, cine SSFP acquisitions were acquired in the left ventricle (LV) to characterize its function and morphology. She had no known prior medical history or cardiovascular symptoms and her only cardiovascular risk factor was a light smoking habit (< 4 pack-years) with normal lipid levels (total-cholesterol = 162 mg/dL, LDL-cholesterol = 94 mg/dL, HDL-cholesterol = 53 mg/dL, triglycerides = 74 mg/dL), normal fasting glucose (4.8 mmol/L) and normal blood pressure (systolic 119 mmHg, diastolic 70 mmHg). Her Framingham risk for cardiovascular ischemic events was very low (less than 1% over 10 years). She had previously been included as a healthy volunteer in other studies and had never been diagnosed with any medical condition. Electrocardiogram (ECG) at inclusion did not show any sign of existing ischemia. Transthoracic echocardiography was considered normal, without any left ventricle wall anomaly. cMRI revealed subendocardial late gadolinium enhancement in one latero-apical segment (Figure 1) compatible with localized silent myocardial infarction. LV mass was 106.2 g (60 g/m^2), LV end diastolic and systolic volumes were respectively 168 mL (95.5 mL/m^2) and 84 mL (47.7 mL/m^2). LV ejection fraction was 50%. Subsequent computed tomography coronary angiography did not show any coronary lesions or plaques and coronary calcium score was 0 (Figure 2). Blood analysis showed normal hemoglobin (Hb) at 13.2 g/dL and Hb electrophoresis revealed a previously unknown HbS proportion of 23.8%. Further genetic analyses finally showed she carried the alpha-thalassemia trait (ATT) (homozygous deletion of locus -3.7) and sickle cell trait (heterozygous for beta-globin mutation 6 Glu-> Val), which had never been diagnosed before. She was later treated in secondary prevention by low-dose aspirin (75 mg/d) and remained asymptomatic during a 6-mo follow-up.

DISCUSSION

Etiology and demographics

Association between alpha-thalassemia and sickle cell trait is frequent with a 10% estimated prevalence, in sub-Saharan Africa from where our patient originates[1,2]. We hereafter discuss this association with cardiovascular outcomes.

Clinical and imaging findings

While alpha-thalassemia major and intermedia (= hemoglobin H disease) have been associated with an increased thrombotic risk[3], alpha-thalassemia minor (= alpha-thalassemia trait) is not considered to increase the risk of ischemic or thrombotic events. Similarly, sickle cell disease is associated with non-atherosclerotic myocardial infarction but sickle cell trait has not been shown to be associated with an increased risk of ischemic events[4].

On the other hand, sickle cell trait carriers have an increased risk of sudden death of unclear pathophysiology[5]. This risk is increased during intensive physical exercise. Hypotheses involve a lowering of pH, an increase in body temperature and concomitant dehydration, all thought to initiate intravascular sickling due to HbS polymerization. This may result in an increase of concentrations of deoxygenized HbS leading to diffuse microvascular obstruction[6].

The most prevalent cause of sudden death in this setting is fatal arrhythmia associated with ischemic

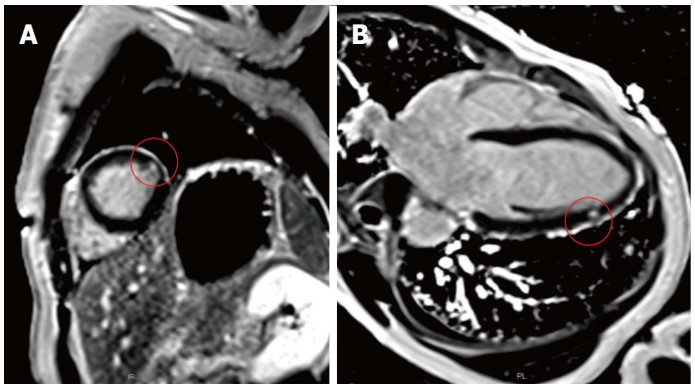

Figure 1 Forty-six-year-old woman, carrier of sickle-cell trait and alpha-thalassemia trait, presenting with silent myocardial infarction. Findings and technique Cardiac magnetic resonance imaging showing (red circle) focal subendocardial late gadolinium enhancement in one apical-lateral segment (75% transmurality). A: Short axis view of the left ventricle with late gadolinium enhancement imaging using a Phase Sensitive Inversion Recovery (PSIR) sequence, 10 min after gadolinium infusion; B: F chamber view in PSIR sequence, 10 min after gadolinium infusion.

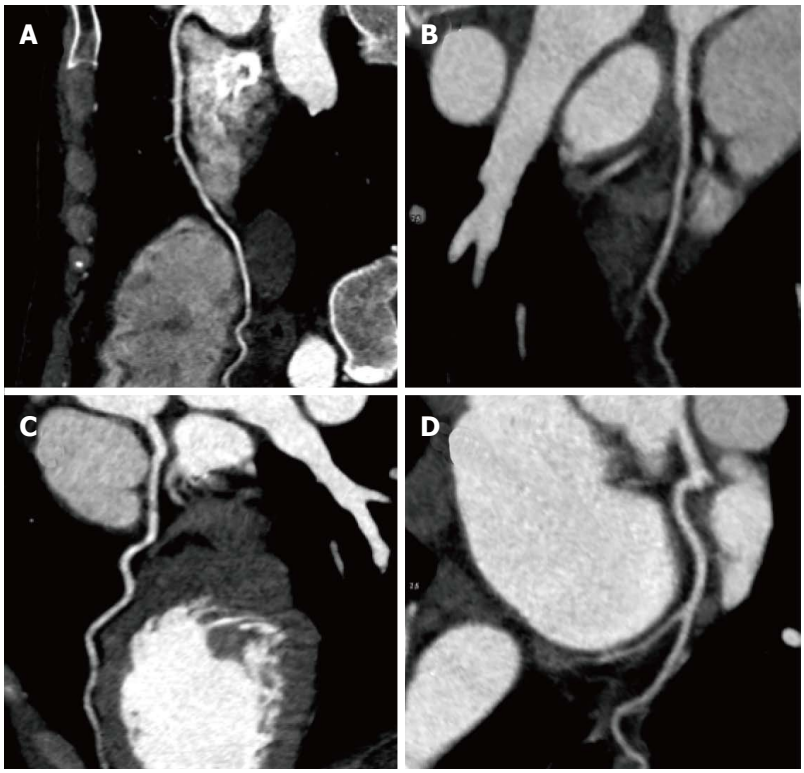

Figure 2 Forty-six-year-old woman, carrier of sickle-cell trait and alpha-thalassemia trait, presenting with silent myocardial infarction. Findings and technique Computed tomography coronary angiography showing normal coronary arteries with no plaque and a global calcium coronary score = 0. A: Right coronary artery; B: Diagonal branch; C: Left coronary artery; D: LIV: Left interventricular coronary artery.

heart disease[7]. Deriving from our case, we hereafter suggest a potential series of events, which may lead to sudden death among sickle cell trait carriers.

Cardiac MRI, a highly sensitive non-invasive myocardial imaging technique, demonstrated the presence of localized silent myocardial infarction. Mechanisms of infarction which have been suggested in the context of sickle cell trait include: (1) rheological factors of altered viscosity and membrane flexibility contributing to microcirculatory stasis; (2) lower platelet survival during sickle cell crisis; and (3) vasospasm[8].

Our patient being a mild smoker, she had an increased procoagulant state[9]. This prothrombotic, proatherogenic state may in turn have favored the formation of micro-thrombi, especially in the distal portion of the myocardial vasculature. Combining this procoagulant state with sickle cell trait may explain why the infarction remained localized without any other signs of atherosclerosis. This is a common feature of infarction among patients presenting with sickle cell disease[4].

Hence, this myocardial scar may represent a substrate for potential ventricular arrhythmia, with physical exercise increasing the risk of sudden death.

Treatment and prognosis

No guideline exists on the use of aspirin for the prophylaxis of ischemic events. A study on prevention of stroke among patients suffering from sickle cell disease is ongoing but results have yet to be published (NCT00178464).

Prognosis of silent myocardial infarction is hard to assess; as by definition, it is asymptomatic. However, with an estimated prevalence of 10% carriers of both sickle-cell and alpha-thalassemia traits in sub-Saharan Africa and a sudden death rate of 0.8/1000 person-year, the annual rate of sudden death associated with this disease would be tremendous.

Differential diagnosis

Coronary artery disease was ruled out by computed tomography coronary angiography, reference imagery in such case of a young woman not presenting with any other cardiovascular risk factor[10].

Silent myocardial infarction can of course be caused by regular cardiovascular risk factors such as smoking in this particular case. Thus, it would be relevant to conduct a large study on carriers of sickle-cell and alpha-thalassemia traits regarding ischemic cardiac disease and independent-related risk factors.

Teaching point

This case raises the importance and pertinence of performing cMRI among asymptomatic patients, and particularly those at higher cardiovascular risk. Patients presenting sickle-cell and alpha-thalassemia traits may be included in this category.

COMMENTS

Case characteristics

Patient was asymptomatic.

Clinical diagnosis

She presented an association of sickle-cell trait and alpha-thalassemia trait, resulting in a silent myocardial infarction.

Differential diagnosis

Myocardial infarction are mostly atherosclerotic, hence, coronary imagery was required.

Laboratory diagnosis

Hemoglobin electrophoresis confirmed the sickle-cell and alpha-thalassemia trait.

Imaging diagnosis

Computed tomography coronary angiography and cardiac magnetic resonance imaging (cMRI) confirmed diagnosis of myocardial infarction and ruled out atherosclerotic cause.

Treatment

Aspirin was given in secondary prevention.

Related reports

Lubega *et al*. Alpha thalassemia among sickle cell anaemia patients in Kampala, Uganda. *Afr Health Sci* 2015; 15: 682-689.

Term explanation

Alpha-thalassemia trait is also known as alpha-thalassemia minor.

Experiences and lessons

Performing cMRI among asymptomatic patients, such as alpha-thalassemia and sickle-cell trait carriers may be acceptable.

Peer-review

This study features the rare finding of myocardial infarction in a case of sickle cell and alpha-thalassemia traits.

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CASE REPORT

Taeniasis: A possible cause of ileal bleeding

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Author contributions: Settesoldi A collected and analyzed the patient's clinical data, wrote and reviewed the manuscript; Tozzi A designed the report and reviewed the manuscript; Tarantino O designed the report and reviewed the manuscript.

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Abstract

Taenia spp. are flatworms of the class Cestoda, whose definitive hosts are humans and primates. Human infestation (taeniasis) results from the ingestion of raw meat contaminated with encysted larval tapeworms and is considered relatively harmless and mostly asymptomatic. Anemia is not recognized as a possible sign of taeniasis and taeniasis-induced hemorrhage is not described in medical books. Its therapy is based on anthelmintics such praziquantel, niclosamide or albendazole. Here we describe a case of acute ileal bleeding in an Italian man affected with both *Taenia* spp. infestation resistant to albendazole and *Helicobacter pylori*-associated duodenal ulcers.

Key words: *Taenia* spp.; Intestinal bleeding; Iron-deficiency anemia; Endoscopy

Core tip: The novel contribution of our paper is to draw attention to taeniasis as a possible cause of gastrointestinal bleeding, since anemia is so far not recognized as a possible sign of taeniasis nor is taeniasis-induced hemorrhage described in medical text books. With this report we describe a case of ileal bleeding most probably caused by this kind of infestation. Our objective is to make clinicians aware of this rare but possible situation. Taeniasis should be therefore taken into account in the differential diagnosis of melena and/or hematochezia.

Settesoldi A, Tozzi A, Tarantino O. Taeniasis: A possible cause

of ileal bleeding. *World J Clin Cases* 2017; 5(12): 432-436 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i12/432.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i12.432

INTRODUCTION

Taenia spp. are flatworms of the class Cestoda, whose definitive hosts are humans and primates. Human infestation (taeniasis) results from the ingestion of raw or undercooked meat contaminated with encysted larval tapeworms (cysticercosis), which subsequently exit the cyst and reach lengths of 3.6-7.5 m in the human gut. In Italy taeniasis incidence is 0.02%-0.04%, while cysticercosis prevalence is 0.02%-2.4%[1]. Taeniasis is relatively harmless and clinically asymptomatic. In sporadic cases it can cause loss of appetite, weight loss, abdominal pain, diarrhea or constipation, dizziness, headaches or nausea. Anemia is not recognized as a possible sign of taeniasis nor is taeniasis-induced hemorrhage described in medical text books[2]. Nevertheless there are some reports in medical literature which consider such associations possible[2-6]. Taeniasis therapy is commonly based on the use of anthelmintics like praziquantel, niclosamide or albendazole. Here we describe a case of acute ileal bleeding in an Italian man affected with both *Taenia* spp. infestation resistant to albendazole and *Helicobacter pylori* (*H. pylori*)-associated duodenal ulcers.

CASE REPORT

In March 2016 a 77-year-old Italian man attended the Emergency Room of San Giuseppe Hospital in Empoli. He was a retired farmer, who had been suffering from hematochezia together with melena for two weeks. His vital parameters were normal. In his medical history there was chronic atrial fibrillation, for which he was taking rivaroxaban 20 mg/d and digoxin 0.125 mg/d, and prior cholecystectomy. He weighed 68 kg, was 170 cm tall (body mass index 23.5). Digital rectal examination revealed the presence of melena. A nasogastric tube was inserted, with no evidence of gastric blood traces. Laboratory tests showed anemia (Hb 5.1 g/dL). The patient underwent blood transfusions and esophagogastroduodenoscopy (EGD), which showed a small hiatal hernia, bile in the stomach and a 10 mm duodenal fibrinous ulcer. We decided to suspend rivaroxaban and start low molecular weight heparin. Continuous intravenous infusion of pantoprazole was administered and the patient was admitted to the Gastroenterology Department.

In the following days he continued to bleed and required further blood transfusions. He also underwent several EGDs, which confirmed the previous findings and allowed us to get biopsies in the antrum for rapid urease test and on the ulcer margins for histology assessment. We also used argon plasma coagulation on the oozing borders of the ulcer, with consequent bleeding cessation. The rapid urease test was positive for *H. pylori* and the patient started eradication treatment. The biopsies of the ulcer margins demonstrated regenerative hyperplasia on productive inflammation.

Despite endoscopic therapy, the patient still complained of melena and hematochezia. He underwent ileocolonoscopy, which showed bright red blood in ileum and colon, without identification of the bleeding source. We performed a contrast-enhanced computed tomography (CT) scan of the abdomen and of the abdominal aorta, which showed no bleeding cause and only minor findings like parietal calcifications of blood vessels, a small hepatic cyst, diffuse moderate intra- and extrahepatic biliary ducts dilation and benign prostatic hyperplasia. We then decided to use wireless capsule endoscopy (WCE), which described two duodenal fibrinous ulcers (5 and 10 mm) without signs of recent bleeding, the presence of a tapeworm, starting from 1 h 45 min until 4 h 28 min after WCE ingestion (Figures 1 and 2) and plentiful dark red blood in the colon, lighter in the proximal regions.

The patient reported only then, that he had occasionally eaten raw beef and that he had taken mebendazole 5 mo before, because of suspected oxyuriasis. The patient received albendazole 400 mg/d for five days, since this drug was suitable for taeniasis and already available in the department.

While on albendazole, he still complained about melena and iron-deficiency anemia (IDA) (Hb 9 g/dL, Hct 27%, RDW-CV 17%, iron 27 μg/dL, ferritin 53 ng/mL), with constant need of blood transfusions. He also stated he had not discharged the head of the tapeworm yet. We performed the last EGD, which demonstrated healing of the ulcers, with no bleeding signs. The second ileocolonoscopy was comparable to the first one, hence we decided to give him a second WCE after discontinuation of albendazole, which demonstrated persistence of the tapeworm starting from jejunum to the whole ileum (last visualization at 4 h 25 min) and plentiful dark red blood in the colon, lighter in the proximal regions (Figures 1 and 2).

We consulted an infectious disease specialist for a change of therapy after albendazole failure. He advised to give the patient niclosamide 2 g in a single administration and then to initiate bowel preparation with macrogol. After niclosamide and bowel preparation we performed the last ileocolonoscopy, which displayed no blood in ileum or colon and 2 non polypoid lesions in the caecum that we removed *via* loop electrosurgical excision procedure. Histology revealed those lesions to be intestinal tubular adenomas with low grade dysplasia.

The day after niclosamide administration, the patient felt a lot better. Melena and rectal bleeding had finally stopped and after two more days he noticed the complete excretion of the tapeworm head. Since his condition was improving, we decided to dismiss him.

He was seen at follow-up visit in mid-June 2016,

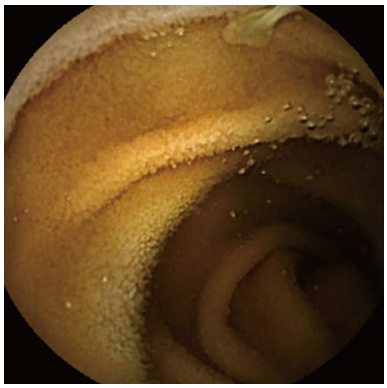

Figure 1 Head of the tapeworm attached to the jejunum at videocapsule endoscopy.

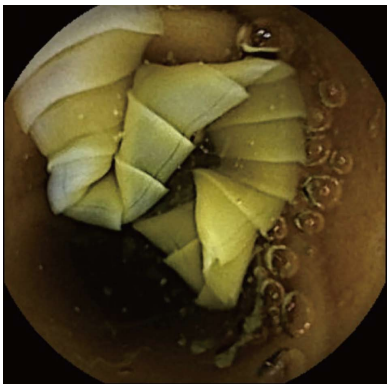

Figure 2 Body of the tapeworm in the ileum at videocapsule endoscopy.

where he stated he was feeling good and had no more rectal bleeding. He performed fecal obscure blood test and *H. pylori* stool antigen test, both showing negative results. His hemoglobin had reached 11.3 g/dL by then, with a positive trend. He underwent ova and parasite fecal exams at 2, 4 and 6 mo after dismission, none of which showed relapse of the infestation.

DISCUSSION

Among the currently accepted causes of iron-deficiency anemia, infestations with *Ascaris lumbricoides*, *Trichuris trichiura*, *Necator americanus* and *Ancylostoma duodenale* are reported, while taeniasis is not mentioned[7].

Likewise, no parasitic infection is officially listed as a cause of upper or lower gastrointestinal (GI) bleeding[8,9].

Even if not conventionally accepted, the association between anemia and/or hemorrhage and taeniasis has already been reported in a few other case reports.

In 1989 Ali *et al*[3] found anemia in 50 urban and rural Egyptians, suffering from various parasitic infestations, among which *T. saginata*.

De Simone *et al*[4] described *T. solium* as the only cause of IDA secondary to acute intestinal bleeding in a woman, who had underwent surgical enterotomy for suspected angiodysplasia.

A case of *T. saginata* infestation causing macrocytic anemia was reported by Vuylsteke *et al*[5] in 2004. The tapeworm and adjacent erosions were seen in the terminal ileum at colonoscopy and the patient recovered after therapy with niclosamide[5].

In 2007 Barnett *et al*[2] published a case of a 7-year old boy suffering from IDA, whose colonoscopy showed taeniasis after repeated normal stool examination. The tapeworm was not regarded as the cause of his anemia and 7 years later anemia recurred. Upper and lower endoscopy were negative and the boy underwent WCE, that found *Taenia* spp. in the mid jejunum, together with ulcers and areas of denuded mucosa.

A case of melena similar to ours was reported by Howell *et al*[6] in 2008. Their patient showed a pylorus ulcer and a vascular duodenal lesion at EGD, which were treated with adrenaline, electrocautery and *H. pylori* eradication, without recovery of the symptoms. A later WCE revealed taeniasis in mid-jejunum, with small erosions, without active bleeding.

In Western countries intestinal parasite infestations are rarely taken into account in the diagnostic work-up of anaemia or GI hemorrhage[4]. In our case anemia could have been attributed at first to the presence of *H. pylori*-associated duodenal ulcers, but melena and hematochezia persisted despite the healing of the ulcers, observed at repeated EGDs and at WCE. While, on the contrary, these two signs stopped after niclosamide therapy and subsequent expulsion of the tapeworm.

The mechanisms that cause digestive bleeding in taeniasis are still poorly understood and could be related to erosions of the bowel mucosa caused by the parasite[4]. Mucosal injury might be determined either directly, by the movement and feeding of the parasite or indirectly, by the host's immune response[5]. Healing of the ulcers has been described after eradication of the tapeworm[2].

Our patient had already taken mebendazole for suspected oxyuriasis 5 mo before. We can speculate that he had taeniasis rather than oxyuriasis and that he saw proglottids instead of pinworms in his feces. Mebendazole is, in fact, not indicated in taeniasis. The majority of people with taeniasis have a single tapeworm in their GI tract and *Taenia* spp. can survive up to 30 years[6].

Stool examination is not a very sensitive test for the diagnosis of taeniasis, because of the need of full maturation of the tapeworm, that can take a lot of months. Differentiation between *T. saginata* and *T. solium* can be obtained from a careful examination of fecal proglottids[6]. Unfortunately we could not perform such examination, since the tapeworm and its proglottids were never collected.

The finding of a tapeworm during an EGD is quite rare. *Taenia* spp. usually attach to the upper jejunum, because their scolex becomes evaginated under digestive enzyme stimuli in that site[10]. Most often, the diagnosis

is made during a colonoscopy or a WCE. According to international guidelines for the management of obscure GI bleeding or unexplained IDA, WCE is indicated after negative upper and lower GI endoscopy[11]. De Simone, Barnett and Howell initially used upper and/or lower endoscopy to diagnose the cause of the blood loss. These procedures didn't reveal the tapeworm. The diagnosis could only be obtained using WCE[2,4,6]. WCE allows physicians to have a look at the entire bowel, especially at those intestinal tracts that are not reachable by EGD or colonoscopy. Our case, as well, highlights the ability of WCE to diagnose taeniasis and to follow abnormalities after treatment[2].

Our patient was a retired farmer who occasionally ate raw beef. We can speculate his rural family background and poor education have led him to take this habit. In any case, we have no evidence for any specific demographics, that could include an increased number of raw meat eaters.

Treatment of taeniasis includes praziquantel (5-10 mg/kg, single-administration) or niclosamide (2 g, single-administration after a light breakfast followed after 2 h by a laxative). Treatment of human cysticercosis includes praziquantel and/or albendazole, corticosteroids and/or anti-epileptic drugs[12]. Asymptomatic cysticercosis requires no treatment. In 1991 De Kaminsky RG treated 56 individuals suffering from taeniasis with albendazole 400 mg for 3 d. All of them discharged the tapeworm and remained stool-negative after 60 and 90 d. Of the 21 *Taenia* spp. recovered, 4 were *T. saginata*, 15 were *T. solium* and 2 could not be identified. Albendazole seemed to be well-tolerated and very effective[13]. Nevertheless albendazole resistance cases have been described. Màrquez-Navarro *et al*[14] reported a case of albendazole failure in a child with 5-year long-lasting infection. Niclosamide is not absorbed by the GI tract. Therefore it has no activity against cysts and is very safe. Its efficacy is high, with cure rates of approximately 90% against *T. saginata* and *T. solium*. Unfortunately, niclosamide is not easy to find[15]. We also had to wait some days to get it, since our hospital pharmacy didn't have it.

Our case underlines the possible association between taeniasis and digestive bleeding. We recommend investigating raw meat consumption in every patients suffering from obscure anemia. In case of positive history, it is advisable to perform ova and parasite fecal tests, whose negative result should not erase the suspicion of a GI infestation. The use of WCE as diagnostic tool in obscure anemia should be supported, as its ability to reveal the presence of tapeworms, after negative EGD and colonoscopy, has been described in this and other case reports. We suggest to be aware of possible drug resistance, which could be demonstrated by the persistence of the tapeworm, and could be overcome through switching therapy. Taking into account the possible association between taeniasis and small bowel bleeding could spare hospitalization days and allow a better and faster recovery of the patients.

COMMENTS

Case characteristics

The man had been suffering of hematochezia and melena for two weeks, together with fatigue, pallor, exertional dyspnea and retrosternal pain receding with rest.

Clinical diagnosis

The patient weighed 68 kg and was 170 cm tall (body mass index 23.5), his vital parameters were good; he showed melena at the digital rectal examination but no gastric blood traces.

Differential diagnosis

Peptic ulcer, Mallory-Weiss lesion, Dieulafoy lesion, neoplasms, esophagitis, gastritis, duodenitis, polyps, inflammatory bowel disease, diverticula, infectious colitis, angiodysplasia, ischemic colitis.

Laboratory diagnosis

Laboratory tests showed anemia (Hb 5,1 g/dL), that was later defined as iron-deficiency anemia (Hb 9 g/dL, Hct 27%, RDW-CV 17%, iron 27 μg/dL, ferritin 53 ng/mL).

Imaging diagnosis

Esophagogastroduodenoscopy (EGD) showed a duodenal fibrinous ulcer, colonoscopy showed blood in ileum and colon, computed tomography scan showed only minor findings, while wireless capsule endoscopy (WCE) showed the presence of a tapeworm in the jejunum- ileum.

Pathological diagnosis

The rapid urease test was positive for *Helicobacter pylori*, the biopsies of the ulcer margins demonstrated regenerative hyperplasia on productive inflammation, the polyps of the colon turned out to be intestinal tubular adenomas with low grade dysplasia.

Treatment

The patient received albendazole 400 mg/d for five days, and then niclosamide 2 g in a single administration.

Related reports

The association between anemia and/or hemorrhage and taeniasis has already been reported in a few other case reports.

Term explanation

Taeniasis is the human infestation of *Taenia* spp., and results from the ingestion of raw or undercooked meat contaminated with encysted larval tapeworms (cysticercosis).

Experiences and lessons

This case underlines the possible association between taeniasis and acute post-hemorrhagic anemia. The authros recommend investigating raw meat consumption in every patient suffering from obscure anemia, and using WCE as a diagnostic tool in case of negative EGD and colonoscopy.

Peer-review

The authors have described a case of gastrointestinal bleeding in a man infestated with *Taenia* spp., that resolved after taeniasis treatment. The novel contribution of this paper is to draw attention to taeniasis as a possible cause of gastrointestinal bleeding that should be therefore taken into account in the differential diagnosis of melena and/or hematochezia.

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CASE REPORT

Do you want to participate in a clinical study as a healthy control? - Risk or benefit?

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Abstract

A healthy woman volunteered to participate as "healthy control" in a study. An increased level of procalcitonin (PCT) was detected and remained elevated on follow-up measurements. As calcitonin levels were elevated as well, thyroid ultrasound was performed which revealed nodes in both thyroid lobes, one of them showing metabolic activity in positron emission tomography-computed tomography scan. To exclude a malignant thyroid cancer despite the negative findings in a fine needle aspiration the patient underwent thyroidectomy and a medullary thyroid carcinoma (MTC) was detected in the right lobe. MTC is a rare endocrine tumor with a poor prognosis once having spread, therefore early detection remains a priority for the outcome. Screening parameter is serum calcitonin, in absence of infection the pro-hormone PCT can be used as a screening parameter as well with high sensitivity.

Key words: Medullary thyroid cancer; Procalcitonin; Thyroid nodes; Endocrinology; Public health; Healthy control

Core tip: A lady participating as healthy control in a study was found to suffer from a medullary thyroid cancer, a type of cancer in total surgical removal before the tumor has spread is the most important prognostic factor. The difficulty is the low diagnostic accuracy of ultrasound and procalcitonin-computed tomography scan, as well as the limitations of fine needle aspiration in a patient with several nodules. This case illustrates the consequences

of volunteering as a "healthy control" in a clinical study. While early detection of the MCT was possible in our patient it paid off for her, but abnormal test results may also cause harm to patients if being false positive and leading to invasive procedures.

Giessen H, Nebiker CA, Bruehlmeier M, Spreitzer S, Mueller B, Schuetz P. Do you want to participate in a clinical study as a healthy control? - Risk or benefit? *World J Clin Cases* 2017; 5(12): 437-439 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i12/437.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i12.437

INTRODUCTION

In our hospital a study to validate the accuracy of a new assay of procalcitonin (PCT) was conducted and a healthy woman working in our hospital was willing to participate in this study as a healthy control.

PCT is excreted by parenchymatous organs in the presence of bacterial infection. As precursor of calcitonin it is elevated in medullary thyroid cancer (MTC) as well as calcitonin. Frozen serum calcitonin can be used as screening parameter, but several non-specialized laboratories limit the use of calcitonin in MTC[1].

CASE REPORT

A 57-year-old, previously healthy woman working in the Department of Clinical Pathology of our hospital volunteered to participate as "healthy control" in a study to validate the accuracy of a new PCT assay. She reported to be in good general health condition without signs of ongoing infection or disease. The patient did not smoke or consume large amounts of alcohol and had no signs of malignancy on physical examination or routine blood analysis. Yet, a markedly increased level of circulating PCT of 0.35 μg/L (normal range < 0.03 μg/L) was detected, which remained elevated on follow-up measurements for the next 2 mo.

Subsequently, calcitonin levels were found to be elevated as well (33 ng/L, normal range < 5 ng/L). A thyroid ultrasound revealed a goiter with small nodules in both thyroid lobes. There were two suspicious thyroid nodules, a small one lateral in the right thyroid lobe (7 mm × 5 mm × 6 mm) and a larger one (10 mm × 10 mm × 13 mm) in the left lobe. A fine needle aspiration (FNA) of the bigger node on the left side was done but neither reveal any malignant cells nor was it positive for calcitonin staining, making the existence of a MTC unlikely. To exclude a gastrointestinal neuroendocrine tumor or a small cell lung cancer, both of which have been reported to ectopically produce PCT as well, we decided to perform a ^{18}F-FDG positron emission tomography-computed tomography (PET-CT), in which the left thyroid nodule detected on ultrasound showed an increased ^{18}F-FDG uptake. There were no other suspicious lesions in the whole body PET-CT scan (Figure 1).

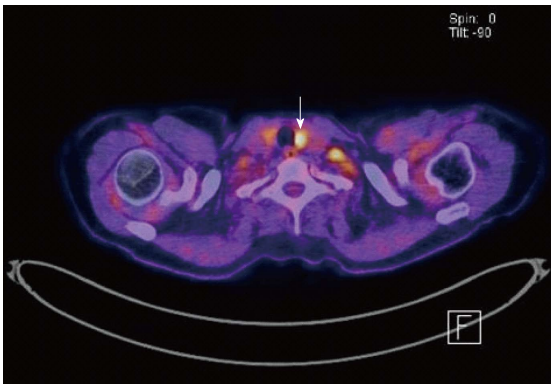

Figure 1 Positron emission tomography-computed tomography scan with ^{18}F-FDG, 2016 February. Arrow: Left thyroid lobe with metabolic active node.

A previously healthy woman willing to support a scientific study was found to have an elevated level of PCT and calcitonin, a goiter, 2 suspicious nodes in the sonography of the thyroid gland with one of them showing metabolic activity in PET-CT scan.

The case was discussed at our internal tumor board, which recommended total thyroidectomy to exclude MTC despite the negative fine needle aspiration as no other cause of elevations in calcitonin and PCT could be found (Figure 2).

The patient agreed to have surgery which went without complications. The histological evaluation of the thyroid gland showed an (incidental) 3 mm papillary microcarcinoma in the left lobe and a 6 mm medullary carcinoma in the right lobe, inconsistent with the active nodule in the left thyroid lobe in PET-CT. No further neck dissection was done due to the relatively low preoperative calcitonin levels.

Two weeks after surgery the patient came back to the endocrine office. Her PCT and calcitonin levels were now undetectable. We recommended close clinical and biochemical monitoring over the next years. Her prognosis is favorable due to the early recognition of the medullary cancer with small tumor volume, in total resection and no signs of metastasis.

DISCUSSION

This case has three key teaching points relevant for clinical care. First, MTC is a rare endocrine tumor accounting for 8% of all thyroid carcinomas[2]. With a five year mortality rate of 50%-70% it represents 14% of all thyroid gland related deaths. Early detection and in total surgical removal before the tumor has spread are the most important prognostic factors to lower mortality in this type of cancer. Due to the poor prognosis of medullary cancer once it has spread, early detection remains a priority[2]. Current guidelines are ambiguous regarding general screening for MTC with calcitonin in the work-up of thyroid nodules, whereas opponents argue it may not be cost-effective[1,3,4]. The challenge in our patient with incidental MTC is the low diagnostic accuracy of ultrasound and the PET-CT scan. In our

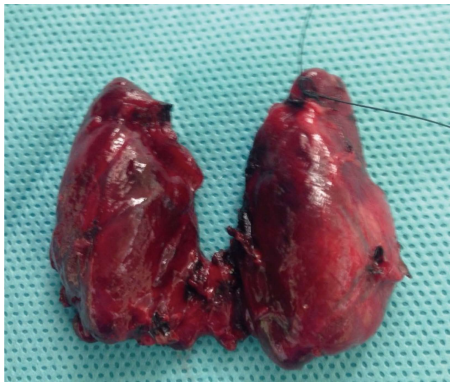

Figure 2 Total thyroidectomie (taken on Jan 17, 2017).

patient, neither test correctly identified or localized the cancer, as retrospectively the metabolically active nodule did not turn out to be malignant. Additionally, fine needle aspiration has limitations particularly sampling bias in a patient with several nodules.

Second, the precursor of calcitonin, PCT became more recently known as an ubiquitously produced biomarker of inflammation and infection. As such it can be used evidence-based in clinical routine guide to diagnosis and antibiotic therapy in respiratory infections and sepsis[5].

As an endocrine tumor marker in the absence of an infection, an elevated ratio of the procalcitonin to calcitonin indicates worse prognosis in patients suffering from MTC[6,7].

Last but not least incidental findings of clinical exams, check-ups, laboratory exams and imaging often occur during diagnostic work-up. This case illustrates possible consequences of volunteering as a "healthy control" in a clinical study. While it most certainly paid off for our patient, abnormal test results may also cause harm to patients if being false positive and leading to invasive procedures. In conclusion, it may become important to discuss risks and benefits when "simply" asking a person to volunteer for a clinical study - even if as an allegedly "healthy control".

ARTICLE HIGHLIGHTS

Case characteristics

Medullary thyroid cancer is a rare cancer that can present with an increased circumference of the throat or a change in voice but is mostly asymptomatic.

Clinical diagnosis

Most medullary carcinoma (MCT) occur sporadic, but in 20% a hereditary pattern (multiple endocrine neoplasia type 2, men 2) is present, a mutation of the RET protooncogene can be found.

Differential diagnosis

MTC is likely to spread lymphogenic to paratracheal and lateral cervical lymph nodes or hematogenous in liver, lungs and bones.

Treatment

The only curative treatment is the total thyroidectomie with removal of all affected tissue in the neck.

Related reports

Systemic chemotherapy with dacarbazine, 5-fluoruracil or doxorubicin has shown a poor response in only 10%-20%.

Experiences and lessons

Regular measurements of serum calcitonin as tumor marker is used and remission is demonstrated by undetectable serum calcitonin.

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CASE REPORT

Embryonal rhabdomyosarcoma in the maxillary sinus with orbital involvement in a pediatric patient: Case report

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Author contributions: Valença AMG, Bonan PRF and de Castro RD designed the report; da Paz AR performed the histopathological and immunohistochemical analyses; de Melo ACR and Ribeiro ILA collected the patient's clinical data; de Melo ACR, Lyra TC and Ribeiro ILA wrote the paper.

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Abstract

This report presents a case of embryonal rhabdomyosarcoma (eRMS) located in the left maxillary sinus and invading the orbital cavity in a ten-year-old male patient who was treated at a referral hospital. The images provided from the computed tomography showed a heterogeneous mass with soft-tissue density, occupying part of the left half of the face inside the maxillary sinus, and infiltrating and destroying the bone structure of the maxillary sinus, left orbit, ethmoidal cells, nasal cavity, and sphenoid sinus. An analysis of the histological sections revealed an undifferentiated malignant neoplasm infiltrating the skeletal muscle tissue.

The immunohistochemical analysis was positive for the antigens: MyoD1, myogenin, desmin, and Ki67 (100% positivity in neoplastic cells), allowing the identification of the tumour as an eRMS. The treatment protocol included initial chemotherapy followed by radiotherapy and finally surgery. The total time of the treatment was nine months, and in 18-mo of follow-up period did not show no local recurrences and a lack of visual impairment.

Key words: Oncology; Embryonal rhabdomyosarcoma; Pediatrics; Maxillary sinus; Chemotherapy

Core tip: This case report is important because it describes the diagnosis trajectory of a rhabdomyosarcoma located in an uncommon region, presenting the steps of the exams performed and their results. The knowledge must be realized with the intention of improving the diagnosis and the clinical conduct, giving greater survival rate and better quality of life to the patient. The early diagnosis was very important in this case, due to the imaging and histopathological exams in question with the association of experienced pathologists.

de Melo ACR, Lyra TC, Ribeiro ILA, da Paz AR, Bonan PRF, de Castro RD, Valença AMG. Embryonal rhabdomyosarcoma in the maxillary sinus with orbital involvement in a pediatric patient: Case report. *World J Clin Cases* 2017; 5(12): 440-445 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i12/440.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i12.440

INTRODUCTION

Rhabdomyosarcoma (RMS) is a malignant mesenchymal tumour of the skeletal myogenic fibres[1,2] and is considered the most common soft-tissue tumour in children and adolescents, responsible for 50% of all soft-tissue sarcomas. It is the second most common paediatric tumour of the head and neck (after lymphoma) and is most commonly located in the cervical-cephalic region or the genitourinary system[3-5].

RMS is histologically classified as embryonal (eRMS), alveolar (aRMS), pleomorphic (pRMS) and spindle cells and sclerotic type (eRMS). The first two subtypes occur in children and adolescents, with the alveolar subtype being more aggressive than the embryonal subtype, while pleomorphic RMS affects adults[5,6]. The first two subtypes (eRMS and aRMS) are diagnosed based on the expression of myogenic markers, such as transcription factors, MyoD, myogenin, myosin heavy-chain structural proteins, skeletal a-actin, and desmin. These markers connect RMS to a skeletal-muscle lineage, but the tumour may also originate from a non-myogenic cell[5,7]. Thus, although RMS usually originates from within a skeletal muscle, it can also develop in areas devoid of muscle tissue, such as the salivary glands, skull base, biliary tree, and genitourinary tract[5,7,8].

Although some eRMS cases were reported before, few cases presented a complete clinical, imaginologic and microscopic documentation, including follow up description. The present study reports a case of eRMS in the left maxillary sinus with invasion of the orbital cavity in a paediatric patient diagnosed and treated at the Hospital Napoleão Laureano in João Pessoa, PB, Brazil.

CASE REPORT

The patient (10 years old, male, mixed race) was admitted to the Hospital Napoleão Laureano, which is a referral hospital for cancer diagnosis and treatment in Paraíba State, presenting with a large swelling and exophthalmos on the left side of the face in addition to a raised and hardened area in the maxillary region that had appeared approximately 25 d prior. The patient presented no fever and reported feeling pain occasionally. The patient's visual acuity, eye structure, and ocular fundus were normal in both eyes (Figure 1).

A computed tomography (CT) scan of the paranasal sinuses was performed with and without intravenously administered contrast. The images showed a heterogeneous (DM = 32 UH) mass with soft-tissue density, measuring 1.5 cm × 6.2 cm × 5.0 cm, occupying part of the left half of the face inside the maxillary sinus, and infiltrating and destroying the bone structure of the maxillary sinus, left orbit, ethmoidal cells, nasal cavity, and sphenoid sinus. Inflammatory sinus disease was present in the left maxillary sinus and left exophthalmos due to the compression exerted on the eye (Figure 2).

Through an incisional biopsy, an oval tissue fragment of light-brown colour and firm-elastic consistency, measuring 1 cm × 0.8 cm × 0.6 cm, was collected from inside the left maxillary sinus. An analysis of the histological sections revealed an undifferentiated malignant neoplasm infiltrating the skeletal muscle tissue (Figure 3).

An immunohistochemical analysis was performed on a biopsied tumour fragment from the left maxillary sinus. The paraffin block was cut into 3-μm sections, which were analysed using an automated method (Ventana Benchmark GX, Roche Diagnostics) with a multimetric detection system (Ventana ultraView Universal DAB detection Kit, Roche Diagnostics). Positive and negative controls confirmed the reliability of the methods. The microscopic examination was positive for the following antigens: MyoD1, myogenin, desmin, and Ki67 (100% positivity in neoplastic cells) (Figure 4), allowing the identification of the tumour as an eRMS.

The treatment plan combined chemotherapy with radiation therapy; chemotherapy was initially performed for a nine-month period (Vincristine, Dactinomycin, and Cyclophosphamide), combined with 20 radiation fractions (50.4 Gy), and followed by surgical ablation of residual mass on maxillary sinus with ocular globe and

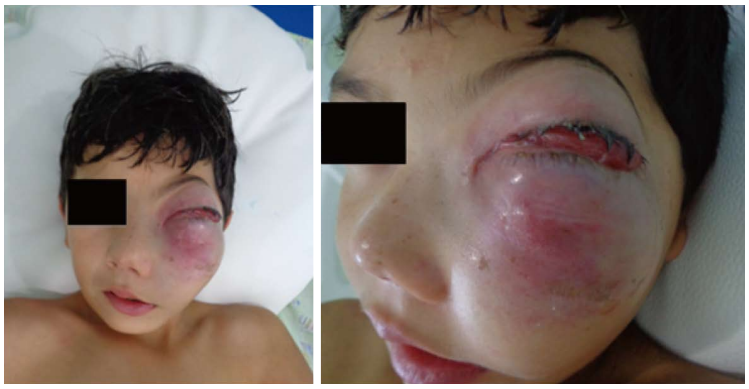

Figure 1 Initial clinical features of the lesion showing a reddish painful firm mass on left side of face with rapid evolution (25 d). This lesion was causing left visual impairment with notorious swelling on facial skin with absence of other obstructive symptoms.

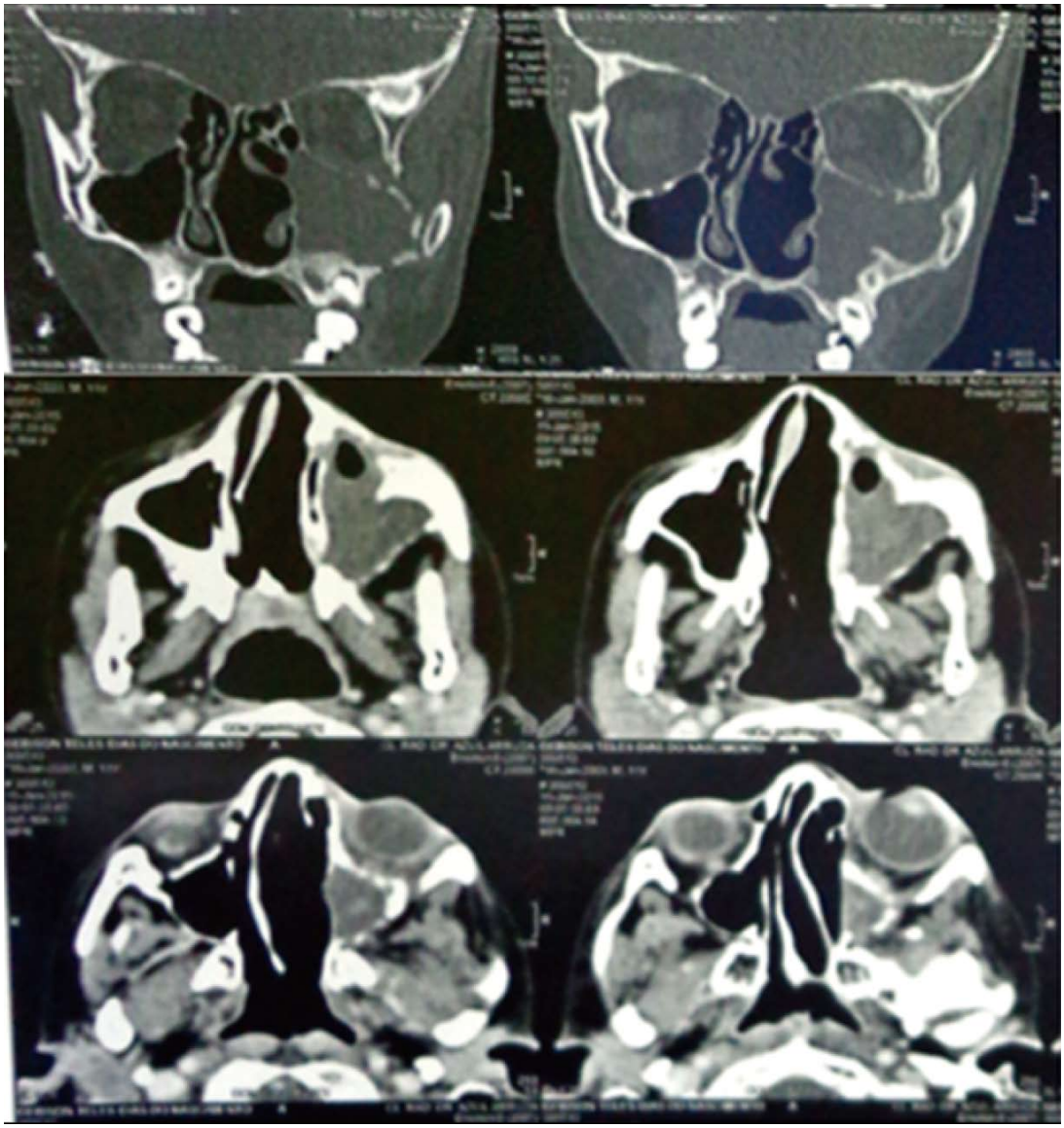

Figure 2 Computed tomography scan of the paranasal sinuses. On coronal view, a diffuse hypodense mass was dislocating lateral wall of left sinus and compressing the inferior border of left orbital structure with tumor invasion. On axial plan, tumor mass was filling the left sinus and a dislocated nasal septum was evident.

optic nerve preservation.

After 2.5 mo of chemotherapy, there was a significant reduction of the tumour mass (Figure 5A). After completion of the treatment (9 mo), the patient

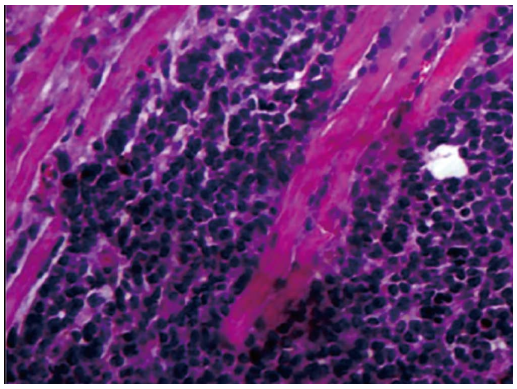

Figure 3 The microscopic slide showed an undifferentiated malignancy with hyperchromatic rounded cells with scarce and eosinophilic cytoplasma infiltrating the skeletal muscle tissue (hematoxylin-eosin, 40 ×).

progressed satisfactorily and, during the follow-up period to date (18 mo), has shown no visual impairment or tumour manifestation in any other region (Figure 5B).

DISCUSSION

The incidence of eRMS is highest in children one to four years old, lower among those 10-14 years old, and lowest among those 15-19 years old[9-11]. The head and neck region is a common site for the development of eRMS. The orbit is the most frequent site[9,12] and is also a common location for tumour extensions of the same histopathology occurring in adjacent cavities[13], such as the maxillary sinus, as reported in the present case.

The cytogenetic characterisation of eRMS is not well established; however, in ⩾ 80% of cases, aRMS is associated with chromosomal translocations between chromosomes 2 and 13 [t (2; 13) (q35; q14)] or chromosomes 1 and 13 [t (1; 13) (q36; q14)] and genetic imbalances that result in the fusion of domains of the transcription factors Pax3 and Pax7 with FOXO1a[2,5,14-16].

The final diagnosis is usually defined based on a tissue biopsy associated with a histopathological and immunohistochemical study[17]. Both aRMS and eRMS express myogenin and MyoD1 (myogenic regulatory nuclear proteins), but the alveolar subtype shows stronger and more generalised myogenin expression than eRMS. The diagnosis of RMS subtypes is important because aRMS is associated with a poorer prognosis, with a greater frequency of disseminated metastases. The immunohistochemical staining of pediatric RMS with antibodies to MyoD and myogenin provides information for a definitive diagnosis. Although almost all cases show nuclear expression of both products, staining for myogenin shows greater clinical utility due to its consistency and association with less nonspecific staining[17].

While it is desirable that pediatric tumours should be identified in their early stages to obtain the best prognosis, the reality is that early diagnosis does not occur in many cases. Additionally, the rapid growth of pediatric tumours makes medical management challenging for combating tumour growth and the complications that can arise from an advanced-stage tumour[18].

The rapid growth of tumour masses in the ocular region, whether derived from the paranasal tissues or otherwise, has been reported in other studies[19,20]. In a case reported by Magrath *et al*[19], a three-year-old male patient also showed swelling in the left eye; however, the tumour dimensions were smaller than those reported here. The growth period was also approximately four weeks; however, the growth originated within the orbit rather than arising from the maxillary sinus tissues, as in the present case. Furthermore, the initial characteristics were consistent with a framework of cellulitis, the aRMS diagnosis was obtained through immunohistochemistry, and tumour remission occurred after one month of treatment with Vincristine, Dactinomycin, and Cyclophosphamide. In a case reported by Chen *et al*[20], the patient was also male and was 13 years old. Exophthalmos of the left eye developed gradually over a two-week period until a doctor was consulted. Upon examination, the patient was diagnosed with aRMS, with destruction of the ethmoid bone, nasal cavity, and orbital cavity but without evidence of distant metastases. A combined treatment protocol consisting of chemotherapy (Vincristine + Actinomycin + Cyclophosphamide) and radiotherapy for high-risk RMS was initiated. After 44 wk of treatment, the tumour regressed completely, and no recurrence was observed at one year after the completion of treatment.

A retrospective analysis of the records of 14 patients by Fyrmpas *et al*[13] showed that the average age of patients with RMS of the sinuses was 7.5 years and that 42.8% underwent surgery before beginning chemotherapy, while 57.2% received chemotherapy and radiation. In addition, intracranial extension and ages greater than 10 years were associated with lower than average survival rates (five-year survival rates, 53.9% for all patients and 83.3% for those who underwent surgery).

The clinical differential diagnosis may be performed with others aggressive connective tissue malignant lesions as Fibrosarcoma, Ewing's sarcoma and Leiomyosarcoma. The final diagnosis is realized through microscopic tests. The prognosis of rhabdomyosarcoma is evaluated according to its clinical, anatomical, histopathological and age characteristics. Normally, the sRMS and aRMS have a good and poor prognosis, respectively. The eRMS of the present case is classified as having an intermediate prognosis lesion[21].

In general, the management of pediatric RMS requires a combination of chemotherapy, radiotherapy, and surgery. Chemotherapy is the first and most important approach to advanced-stage tumours, such as that described here. Tumours diagnosed at an early stage can be treated with a radical surgical approach because the function and cosmetic appearance can

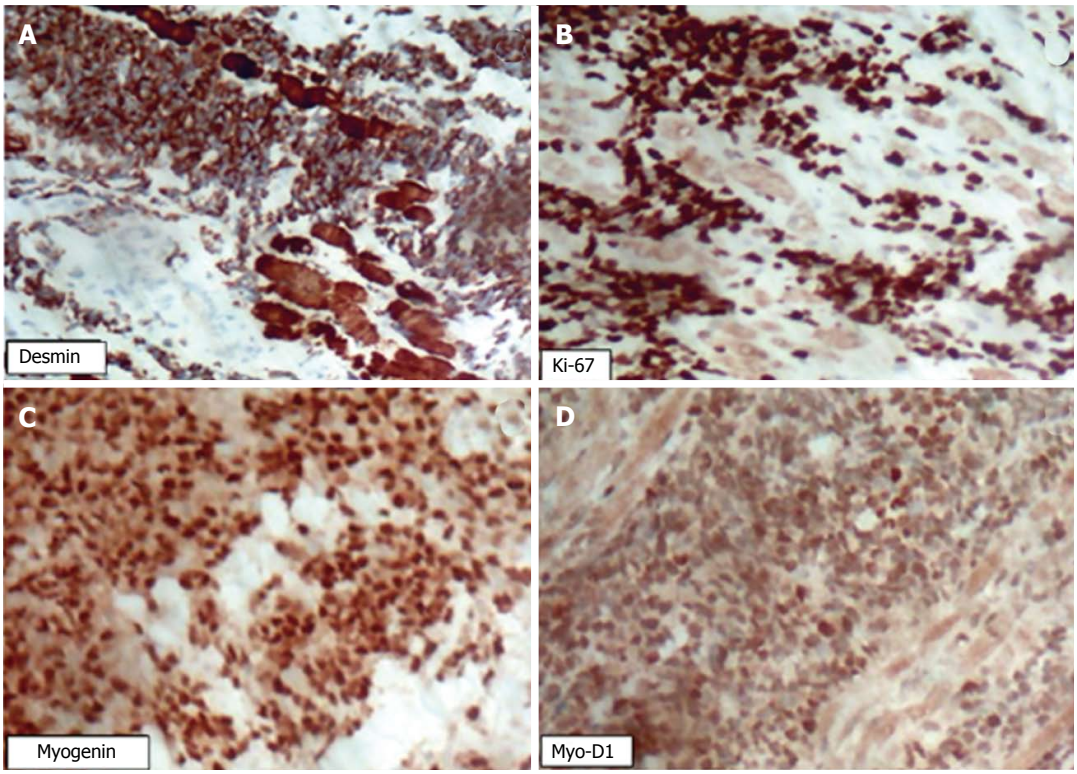

Figure 4 An immunohistochemical analysis was performed on a biopsied tumour fragment from the left maxillary sinus. A: Immunohistochemical analysis showed positiveness to anti-Desmin antibody with dual cytoplasmatic and nuclear staining; B: The same pattern was observed against anti-Ki67 (B) showing intense positiveness and high rate of cell proliferation; C and D: Anti-myogenin and MYO-D1 were positively found on nuclear staining leading to RMS lineage supposition.

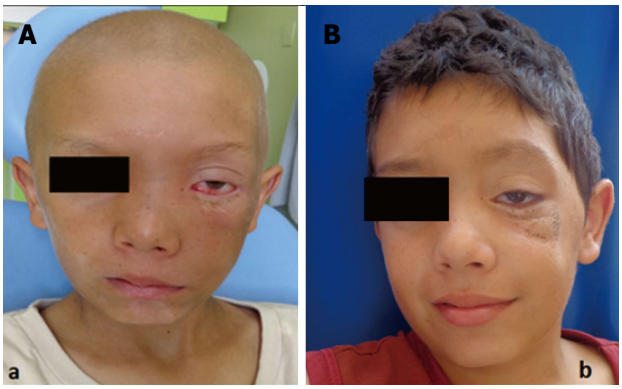

Figure 5 Monitoring of the patient after the period of 2.5 mo of chemotherapy and after completion of treatment (18 mo). A: Monitoring of the patient after the period of 2.5 mo of chemotherapy; B: Monitoring of the patient after completion of treatment (18 mo).

possibly be preserved.

This paper focused a single clinical case which could not be extrapolated to all cases of RMS on head and neck. However, due to scarcity of analogous clinical cases and needing to better comprehend this condition, this report could be useful for clinical practice, including differential diagnosis options and diagnosis by clinical or microscopic similarities. It is vital that health professionals are aware of the early signs of cancer in paediatric patients and have sufficient knowledge of efficient referral procedures to paediatric cancer diagnosis and treatment units so that children and adolescents will not suffer the consequences of late diagnosis and receive a less aggressive treatment approach.

COMMENTS

Case characteristics

The patient presented occasionally pain, large swelling and exophthalmos on the left side of the face in addition to a raised and hardened area in the maxillary region that had appeared approximately 25 d prior.

Clinical diagnosis

According to the clinical examination, the patient's visual acuity, eye structure, and ocular fundus were normal in both eyes.

Differential diagnosis

The differential diagnosis are others aggressive connective tissue malignant lesions as Fibrosarcoma, Ewing's sarcoma and Leiomyosarcoma.

Imaging diagnosis

The computed tomography showed a heterogeneous mass occupying part of the left half of the face inside the maxillary sinus, and infiltrating and destroying the bone structure of the maxillary sinus, left orbit, ethmoidal cells, nasal cavity, and sphenoid sinus.

Pathological diagnosis

An analysis of the histological sections revealed an undifferentiated malignant neoplasm infiltrating the skeletal muscle tissue.

Treatment

The treatment plan combined chemotherapy with radiation therapy and followed by surgical ablation of residual mass on maxillary sinus with ocular globe and

optic nerve preservation.

Related reports
To our knowledge, there aren't many papers about embryonal rhabdomyosarcoma (eRMS) that describes pathological, immunohistochemical and surgical findings of a clinical case in the literature.

Term explanation
Regarding the trajectory of this case, everything occurred according to the terms.

Experiences and lessons
This report helps to further understand eRMS in terms of diagnosis, clinical presentation, treatment and prognosis.

Peer-review
This is a well written case report.

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CASE REPORT

Topiramate induced peripheral neuropathy: A case report and review of literature

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Abstract

Drug-induced peripheral neuropathy had been rarely reported as an adverse effect of some antiepileptic drugs (AEDs) at high cumulative doses or even within the therapeutic drug doses or levels. We describe clinical and diagnostic features of a patient with peripheral neuropathy as an adverse effect of chronic topiramate (TPM) therapy. A 37-year-old woman was presented for the control of active epilepsy (2010). She was resistant to some AEDs as mono- or combined therapies (carbamazepine, sodium valproate, levetiracetam, oxcarbazepine and lamotrigine). She has the diagnosis of frontal lobe epilepsy with secondary generalization and has a brother, sister and son with active epilepsies. She became seizure free on TPM (2013-2017) but is complaining of persistent distal lower extremities paresthesia in a stocking distribution. Neurological examination revealed presence of diminished Achilles tendon reflexes, stocking hypesthesia and delayed distal latencies, reduced conduction velocities and amplitudes of action potentials of posterior tibial and sural nerves, indicating demyelinating and axonal peripheral neuropathy of the lower extremities. After exclusion of the possible causes of peripheral neuropathy, chronic TPM therapy is suggested as the most probable cause of patient's neuropathy. This is the first case report of topiramate induced peripheral neuropathy in the literature.

Key words: Topiramate; Peripheral neuropathy; Sodium channel blockade; Antiepileptic drugs

Core tip: Peripheral neuropathy is a rare adverse effect of short- or long-term use of antiepileptic drugs (phenytoin, phenobarbital, carbamazepine, valproate, gabapentin, levetiracetam and lacosamide). This is the first case report of topiramate induced peripheral neuropathy (TIPN). Manifestations of TIPN are distal paresthesia, areflexia, sensory deficits and reduced amplitudes and nerve

conduction velocities of motor and sensory peripheral nerves of the lower extremities indicating demyelinating and axonal neuropathies. The risk is greater with long-term therapy. The mechanisms of TIPN may involve impairment of nerve function through blocking of sodium voltage channels, enhancement of gamma amino butyric acid inhibitory neurotransmission or others.

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INTRODUCTION

Topiramate (TPM) is a broad-spectrum antiepileptic drug (AED) to treat varieties of seizures in adults and children. TPM is recommended as add-on or mono-therapy to treat patients two or more years old with generalized tonic clonic epilepsy or focal epilepsy with or without secondary generalization which are refractory to treatment with other AEDs; and for Lennox-Gastaut syndrome (LGS)[1]. TPM has been approved by the United States Food and Drug Administration (FDA) in combination with phentermine for weight loss[2] and for migraine prevention[3]. TPM has also off-label uses, *i.e.*, not mentioned in patients' leaflet and/or prescribing information] which include treatment of bipolar disorder[4]; borderline personality disorder[5]; alcoholism[6]; and antipsychotics-induced weight gain[7]; and as a mood stabilizer[8].

TPM has many adverse side effects. Some are very common (> 10% incidence) including dizziness, weight loss, paraesthesia in the face, mouth and extremities (pins and needles which occur in 12%-14% of patients), somnolence, nausea, diarrhea and fatigue. Others are common (1%-10% incidence) including disturbance in attention, memory deficits, amnesia, cognitive disorder, psychomotor slowing, abnormal coordination, tremors, sedation, vomiting, vertigo, tinnitus, dry mouth, abnormalities of taste and abdominal discomfort. However, most of these adverse effects are mild/moderate, transient and related to higher doses and/or rapid dose titration rate. Thus, these side effects can be reduced or prevented by starting TPM at low doses and gradually increasing the dosage[9]. Also, TPM has some rare and serious side effects which necessitate drug withdrawal and replacement by alternative, these include acute angle glaucoma, acute myopia, decreased sweating and increase in body temperature, confusion, speech arrest[10], manifest metabolic acidosis[11] and urolithiasis of clinical importance[12]. Most of these side effects are related to the carbonic anhydrase enzyme inhibition properties of TPM.

Review of the literature shows that AEDs therapy is rarely associated with peripheral neuropathy. Peripheral neuropathy is a rare adverse effect of phenytoin (PHT) as evidence by clinical and experimental studies[13,14]. It had been reported with short-term treatment (hours to weeks) with PHT in toxic[15-18] or non-toxic doses[19-21] and with long-term (⩾ 5 years) PHT therapy[22-25]. Peripheral neuropathy had been also reported with therapy with other AEDs as carbamazepine (CBZ)[26-28], phenobarbital (PB)[27], sodium valproate (VPA)[26,27,29,30], gabapentin (GPN)[31], levetiracetam (LEV)[32] and lacosamide (LCM)[33]. There is no previous report for peripheral neuropathy induced by TPM.

CASE REPORT

A 37-year-old well-nourished woman presented at the year 2010 with frequent attacks (two or more ictal attacks per week) of generalized tonic clonic convulsions. Clinical, electroencephalography (EEG) and magnetic resonance imaging diagnosis are consistent with idiopathic frontal lobe epilepsy with secondary generalization. The patient has a brother, sister and son with chronic active epilepsy. The patient tried different AEDs as mono- or combined therapies [CBZ and/or VPA, LEV or lamotrigine (LTG)] but with no significant improvement. TPM (100 mg BID) was started (2013) as monotherapy (associated with gradual withdrawal of the other administered AEDs) and the patient became seizure free few months after the start of TPM. The patient experienced some transient side effects which included sense of pins and needles in the face, mouth, body and limbs; myalgia, muscle spasms (cramps) and increased forgetfulness which improved spontaneously within weeks to few months. Laboratory investigations demonstrated hypocalcemia (serum Ca^{2+} = 7.6 mg/dL). Reassurance of the patient was done and muscle spasms and myalgia disappeared with vitamin D and calcium supplementations. Two years after starting TPM therapy (2015), the patient developed persistent distal numbness in the lower extremities. Neurological examination revealed presence of diminished knee and ankle tendon reflexes, diminished pain and temperature sensation of stocking distribution and decreased vibration perception in the lower limbs. Nerve conduction velocity studies of the median, ulnar, common peroneal, posterior tibial and sural nerves revealed prolonged distal latencies of the tibial nerves (right = 5.9 ms, left = 6.2 ms), reduced their motor conduction velocities (MCVs) (right = 42.7 m/s, left = 35.9 m/s) and amplitudes of their motor action potentials (MAPs) (right = 1.14, 1.25 mV, left = 1.39, 1.10 mV); prolonged distal latencies of sural nerves (right = 6.48 ms, left = 5.67 ms), reduced their sensory conduction velocities (SCVs) (right = 24.7 m/s, left = 28.2 m/s) and amplitudes of their sensory action potentials (SAPs) (right = 14.00 μV, left = 26.6 μV) (Figure 1). The diagnosis of TPM induced peripheral neuropathy was probably suggested after

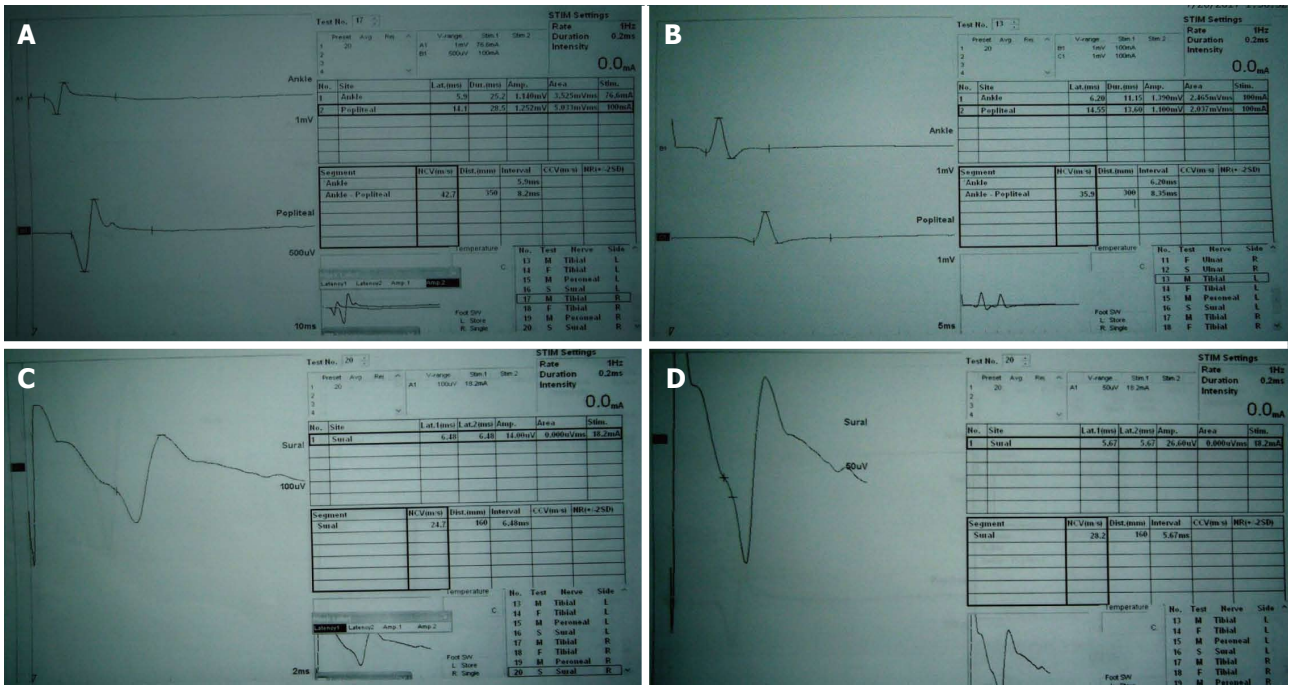

Figure 1 Nerve conduction velocity study traces of the right (A) and left tibial (B) nerves and right (C) and left sural (D) nerves show prolonged distal latencies, reduced motor and sensory conduction velocities and reduced motor and sensory action potentials (amplitudes).

exclusion of the general and common risk factors for the development of peripheral neuropathy which include diabetes, toxins, nutritional disorders (*e.g.*, B-vitamin deficiency) and infectious (*e.g.*, tuberculosis and HIV), connective tissue and metabolic diseases and according to the Naranjo adverse drug reaction (ADR) probability scale (ADR score = 7)[34]. Vitamin B supplementations (thiamine, riboflavin, pyridoxine, cyanocobalamin and folic acid) and anti-oxidants (lipoid acid, primrose oil and vitamin E) were prescribed for the patient for several weeks but no improvement was observed in peripheral neuropathy manifestations. The decision to continue on TPM was discussed with the patient because she is well-controlled (seizure free) on TPM monotherapy after failure to control seizures with other AEDs, no worsening of peripheral neuropathy with time and this side effect was well tolerated by the patient.

This study was conducted according to the principles established in Helsinki and approved by Assiut University Hospital ethics committee. Informed written consent was obtained from the patient to publish the details of her clinical history, laboratory and neurophysiological data.

DISCUSSION

Nearly 12%-14% of patients on TPM commonly experience transient parasthesia in the face, mouth and extremities early during treatment[9] which disappears spontaneously or with the use of potassium therapy[35], however, it may be severe and intolerable in some patients and resulted in discontinuation of TPM[9]. Some evidence suggests that the tendency to cause paresthesia is due to TPM effect on an enzyme called carbonic anhydrase which is an enzyme found in nerve tissue, and probably helps nerve cells talking to one another[35]. However, it seems that another cause of parasthesia may occur with chronic TPM therapy due to the effect of TPM on peripheral nerves. This is the first report of presence of peripheral neuropathy in a patient with epilepsy due to chronic therapy with TPM. Peripheral neuropathy induced by TPM is manifested by parathesia in both lower limbs, decreased ankle jerks, stocking distribution of hypesthesia and delayed distal latencies, reduced nerve conduction velocities of motor and sensory peripheral nerves and reduced amplitudes of motor and sensory action potentials of the peripheral nerves of the lower limbs, indicating demyelinating and axonal peripheral neuropathy. As the patient is seizure free on TPM after several years of ineffective other AEDs therapies, I was unable to do re-challenge testing (stopping and re-staring the treatment to be sure that it was the cause peripheral neuropathy). Only reassurance of the patient was done and no specific treatment was prescribed as the patient has mild paraesthesia and non-progressive peripheral neuropathy.

In general, AEDs are used to treat cortical hyper-excitable states which result in epilepsy and peripheral nerve hyperexcitability which both result in neuropathic pain. Regarding TPM, some experimental and clinical studies demonstrated its efficacy to treat neuropathic pain. Lopes *et al*[36] demonstrated the antinociceptive effect of oral administered doses of TPM (80 mg/kg) in the models of nociception induced by chemical (formalin) or thermal (hot plate) stimuli. Siniscalchi *et al*[37] reported complete improvement of idiopathic

glossodynia in a 65-year-old woman with 4 mo history of glossodynia with TPM after failure of CBZ or GPN. Glossodynia is a painful sensation in the mouth, throat and especially the tongue due to altered excitability in the trigeminal nociceptive pathway at peripheral and/or central nervous system levels. In another study, Siniscalchi *et al*[38] reported improvement of dysesthetic pain with TPM (150 mg/d within 8 mo) in a 42-year-old woman with 8 years history of multiple sclerosis. Erdoğan *et al*[39] observed a significant decrease in the strength duration time constant (which provides an indirect idea about the persistent, paranodal sodium channels and may indirectly reflects the peripheral nerve excitability) but did not observe significant affection of median nerve motor and sensory conduction parameters after the initiation of TPM for 4 wk, reflecting a reduction in the peripheral nerve excitability induced by TPM.

In the literature, peripheral neuropathy had been reported as a rare adverse effect with short-term treatment (hours to weeks) with PHT in toxic[15-18] or non-toxic doses[19-21] and with long-term (months to years) PHT therapy[22-25]. Acute peripheral neuropathy induced by PHT is very rare and reversible side effect[17,19-24]. Hopf *et al*[19] reported slight but significant reduction in the mean ulnar nerve conduction velocity in 13 patients after the intake of 500-600 mg PHT per day for a week which was not correlated with serum PHT levels. Lovelace and Horwitz[40] reported decrease in motor and sensory conduction velocities of the peripheral nerves without any symptoms (occult) during PHT administration among patients with epilepsy. Birket-Smith and Krogh[15] reported peripheral neuropathy with PHT level more than 20 μg/mL, however, no correlation was observed between the clinical toxicity severity and the degree of conduction velocity abnormalities. Meienberg *et al*[17] reported acute severe mainly motor polyneuropathy in the legs and cerebellar symptoms after treatment of a 34-year-old epileptic male with high doses PHT to control status epilepticus although this patient was treated for more than ten years with an average of 300 mg PHT and 200-300 mg phenobarbital (PB) daily. Fujiwara *et al*[24] reported prolonged distal latency of the tibial nerve and decreased mixed nerve action-potential amplitudes of the posterior tibial and median nerves. Wessely *et al*[20] reported an axonal polyneuropathy with minimal reduction in motor nerve conduction and a considerable extension of distal latency and diminution of compound action potential in 5 patients who were treated with long-term PHT for epilepsy. In 4 cases, the symptoms appeared following treatment of status epilepticus with additional PHT medication. All patients had acute symptomatic psychosis, diffuse slowing of the curves in the EEG and cerebellar signs and two of them additionally complained of objective polyneuropathy. Nerve biopsy in one patient showed concentric lamellar bodies coming from the axon with intact myelin sheaths. Ramirez *et al*[18] reported a 47-year-old man with clinical and electrophysiological signs of peripheral neuropathy after 30 years treatment with PHT (300 mg/d, the blood levels were 31-38 μg/mL). A sural nerve biopsy showed loss of large myelinated nerve fibers and non-random clustered distribution of segmental demyelination, remyelination and axonal shrinkage. Clinical and electrophysiological improvement was observed within 16 mo of PHT withdrawal. Yoshikawa *et al*[21] reported an 18-year-old girl who developed distal lower extremity paresthesia in a stocking distribution, motor weakness, absent Achilles tendon reflexes, slightly reduced sensory conduction velocities and mild prolongation of distal latencies in the lower extremities just few hours after the administration of PHT to control epilepsy. Discontinuation of PHT resulted in gradual disappearance of the symptoms and returning of the distal latencies and sensory conduction velocities to normal. Le Quesne *et al*[14] demonstrated acute slowing of motor nerve conduction velocity in guinea pigs after only 3-4 d of PHT administration. Furthermore long-term PHT administration can cause of peripheral neuropathy which is more frequent than acute forms. Eisen *et al*[22] reported peripheral neuropathy with the use of PHT which was correlated with PHT level. Chokroverty and Sayeed[16] reported significant reduction in the mean motor conduction velocity of posterior tibial nerves of epileptic patients treated with PHT for more than 10 years or in patients with serum PHT level above 20 μg/mL. Dobkin[23] reported dysesthesia and sensory and reflex loss in the legs in a patient treated for seizures with PHT in the therapeutic range for one year. Discontinuation of PHT resulted in resolution of peripheral neuropathy. Mochizuki *et al*[25] reported slowed motor conduction velocities of the ulnar (33.3%) and posterior tibial nerves (23.8%), followed by slowed sensory conduction velocities of the sural nerves (20%), lowered H/M ratio (14.3%), and slowed motor conduction velocities of the peroneal (14.3%) and median (14.2%) nerves in children with epilepsy. The authors observed significant correlations between the total dosage and duration of therapy with PHT and the reduction of motor conduction velocity in the posterior tibial nerve.

Peripheral neuropathy had been also reported with other AEDs therapy as CBZ[26-28], PB[27], VPA[26,29,30], GPN[31], LEV[32] and LCM[33]. A review of the literature showed that reflex sympathetic dystrophy (RSD) is precipitated by PB in 10%-30% of cases[41,42]. RSD syndrome is clinically characterized by pain and edema of one or more extremities, trophic skin changes and vasomotor instability. Swift *et al*[29] reported that 16.7% of epileptic patients may develop peripheral neuropathy with different AEDs which is characterized by stocking hypesthesia, reduced Achilles reflexes, slowing of peroneal and sural nerve conduction velocities and prolonged or absent H reflexes and F responses. Geraldini *et al*[26] reported slowing of the peroneal and median motor nerve conduction velocities and median sensory nerve conduction velocities with CBZ, PB and PHT. Significant correlation was identified

between the slowing of the conduction velocity and the daily dose of CBZ but not its serum drug level or duration of treatment. In the study done by Bono *et al*[27] on 141 adult patients treated for less than 6 mo with standard daily doses of the commonest AEDs, the authors reported that 53% of patients had one or more symptoms of polyneuropathy (paresthesias being the most common complaint). The neurologic examination was abnormal in 32%. Electrophysiologic findings in two or more separate nerves were abnormal in 77 patients (54.6%); of these, 27 (19.1%) had abnormal neurologic findings and 21 (14.9%) also had symptoms of polyneuropathy. Sensory functions were the most frequently impaired. Axonal damage with secondary myelin changes was noted in sural nerve biopsies of patients on CBZ, PB and PHT. A correlation was noted between polyneuropathy and combined therapy with two or more AEDs. Gould[31] reported a 58-year-old man who developed a painful polyneuropathy while being treated with GPN although GPN is considered an effective treatment for neuropathic pain syndromes. Kapoor *et al*[32] reported a case of polyneuropathy induced by LEV which improved with discontinuation of LEV. Boylu *et al*[28] reported mild prolongation in the distal latency of median sensory, ulnar sensory and sural nerves with diminished nerve conduction velocities with chronic CBZ therapy but not with VPA, oxcarbazepine (OXC) or TPM. Marusic *et al*[30] reported a 26-year-old man with weakness of flexion and abduction of the right arm and loss of sensation in the skin over the lateral upper right arm and reduced amplitude and prolonged latencies in the right axillary nerve because of a suicide attempt with VPA overdose (serum VPA level = 2896 μmol/L; therapeutic range = 350-690 μmol/L). In an experimental study, Zafeiridou *et al*[33] observed a differential effect for LCM, PHT and TPM on peripheral nerve excitability. The authors reported inhibition of compound action potential of the sciatic nerve of an adult rat after 48 h period of LCM exposure at concentrations higher than the therapeutic level (> 25 μg/mL). An acute and immediate increment of the latency and decrement of the amplitude of the nerve compound action potential were observed at LCM concentrations of 62.57-125.15 μg/mL. However, in contrast to LCM, PHT resulted in an acute decrement in the amplitude of the nerve compound action potential as well as an increment in the latency of the compound action potential even at sub-therapeutic levels (5 μg/mL). Reduced compound motor action potential amplitude was also observed with TPM at concentration of 33.94 μg/mL (supra-therapeutic).

The mechanism (pathogenesis) of PHT induced peripheral neuropathy is not well known. Experimental studies demonstrated a depressant effect of PHT on peripheral nerves[13] which has been attributed to the direct toxic effect of the drug on peripheral nerves and/or due to blockage of sodium channels which is its main anticonvulsant mechanism of action. Korey[43] demonstrated an inhibitory effect of PHT on the giant axon of the squid which was made hyperexcitable by low calcium and magnesium levels. Eisen *et al*[22] reported a primary axonal shrinkage and secondary demyelination with PHT. Long *et al*[44] and Hansen *et al*[45] demonstrated that peripheral neuropathy induced by PHT was related to the subnormal serum folate in association with megaloblastic anemia. We suggest that peripheral neuropathy induced by TPM may be related to its anticonvulsant mechanism of action which is multifactorial and involve blockade of voltage-dependent sodium channels (similar to PHT); inhibition of high-voltage-activated calcium channels; potentiation of GABAergic transmission through GABA-A receptors; inhibition of excitatory pathways through an action at α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) AMPA/kainate receptors sites and inhibition of carbonic anhydrase isoenzymes[1].

We report a patient with peripheral neuropathy after chronic therapeutic dose of TPM. However, this adverse effect was mild, static and tolerated by the patient and did not disappear with vitamin B supplementations. There is also a need for experimental and clinical studies to identify the effect of TPM on peripheral nerves and to identify the mechanism(s) of TPM induced peripheral neuropathy.

COMMENTS

Case characteristics

A 37-year-old woman presented with frontal lobe epilepsy with secondary generalization which was intractable to different antiepileptic medications as mono- or combined therapy. Topiramate (TPM) monotherapy significantly controlled the patient's seizures. After two years of therapy with TPM, the patient developed paresthesia, diminished Achilles tendon reflexes, stocking hypesthesia and delayed distal latencies, reduced conduction velocities and amplitudes of action potentials of posterior tibial and sural nerves.

Clinical diagnosis

Peripheral neuropathy probably induced by long-term TPM therapy.

Differential diagnosis

Other causes of peripheral neuropathy which include diabetes, toxins, nutritional disorders (*e.g.*, B-vitamin deficiency) and infectious, connective tissue and metabolic diseases.

Laboratory diagnosis

Demyelinating and axonal peripheral neuropathy of the tibial and sural nerves.

Treatment

Reassurance of the patient and continue therapy with TPM because the patient is well-controlled (seizure free) on TPM therapy, no worsening of the course of peripheral neuropathy with time and this side effect was well tolerated by the patient.

Related reports

Peripheral neuropathy has been reported as adverse side effect of some antiepileptic drugs (AEDs) including phenytoin, phenobarbital, carbamazepine, valproate, gabapentin, levetiracetam and lacosamide. Most of case reports in the literature are peripheral neuropathy induced by short-term or long-term treatment with phenytoin. There is no previous report for TPM induced peripheral neuropathy.

Term explanation

Peripheral neuropathy is a rare adverse effect of short- or long-term use of AEDs. The risks for peripheral neuropathy induced by AEDs include the high drug doses, high drug serum levels and longer duration of therapy. Some of AEDs may induce acute or severe peripheral neuropathy which necessitates drug withdrawal and use of alternative. There is no previous report of TPM induced peripheral neuropathy. This study is the first report of peripheral neuropathy which is most probably induced by long-term use of TPM.

Experiences and lessons

According to the Naranjo adverse drug reaction probability scale, it seems that chronic TPM therapy is the most probable cause of patient's neuropathy. Peripheral neuropathy induced by TPM is mild/moderate in severity, non-progressive and not bothersome to patients and may not necessitate drug discontinuation.

Peer-review

The presented case is interesting.

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