Triple Combination with Direct Acting Antivirals in the Treatment of Hepatitis C Does not Prolong the QT Interval

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ABSTRACT

Aims: Antiviral drugs are considered as potentially cardiotoxic, due to prolongation of QT interval which may affect incidence of severe ventricular arrhythmias. The main aim of this retrospective study was to assess the influence of treatment by three antiviral drugs on QT interval and to find patients who are at an increased risk of developing malignant ventricular arrhythmias.

Methods: The study included 23 patients (14 men, 9 women) who were treated with a combination of interferon alpha, ribavirin, and an NS3/4A protease inhibitor. The parameters from the 12 leads electrocardiograms were evaluated before treatment, and then 3 ± 1 and 6 ± 1 months after treatment.

Results: Heart rate (HR) 69 ± 12 / min and corrected QT interval (QTc) 412 ± 35 ms were obtained before the treatment and there was not observed a significant prolongation of intervals after 3 months (HR 72 ± 11 / min, QTc 412 ± 33 ms) and after 6 months (HR 64 ± 12 / min, QTc 405 ± 28 ms) respectively. In total QTc interval was prolonged from the baseline in 53% and in 43% of the patients 3 months respectively 6 months after treatment. A QTc prolongation over of 450 ms and new treatment-related repolarization change was noted in 1 (4%) patient.

Conclusion: The study demonstrates that a combination therapy of 3 antiviral drugs does not significantly prolong the QTc interval and does not cause severe pathological changes on the ECG. Patients undergoing this treatment are not at risk of developing heart disease as an undesirable side effect.

KEYWORDS

hepatitis C virus; HCV; QT interval; NS3/4A protease inhibitor; DAAs

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INTRODUCTION

The Hepatitis C virus (HCV) affects about 130–170 million people worldwide, which is approximately 3% of the population (1). About 55–85% of affected patients will develop chronic hepatitis, 30% cirrhosis and 2% hepatocarcinoma (2). Chronic HCV infection is one of the leading causes of liver-related death and it is the primary reason for having a liver transplant in many countries. The goal of HCV treatment is the eradication of the virus, which is confirmed in the laboratory as undetectable viral RNA 12 weeks after ceasing treatment. The established treatment strategy contains interferon alfa and ribavirin. There are several documented clinical cases which demonstrate dilated cardiomyopathy, conduction system disturbances and pericarditis (3–5). Otherwise, cardiotoxicity of a combination INF-alfa and ribavirin is rare and may be used safely in patients without cardiac disease (6). However, this strategy is less effective in genotypes 1 and 4. In 2011 were introduced NS3/4A protease inhibitors, also known as direct-acting antivirals (DAAs), that target different steps in the HCV life cycle – boceprevir, telaprevir and later a second-generation drug simeprevir (7–9). NS3/4A inhibitors are given in triple combination with interferon alfa and ribavirin. This strategy is more effective in sustained viral response, but also provides more interactions and side effects.

An important potential drugs side effect includes abnormalities in cardiac repolarization resulting in QT prolongation. QT interval prolongation is associated with an increased risk of life-threatening polymorphic ventricular tachycardias called Torsades de Pointes (TdP), which can lead to ventricular fibrillation and sudden cardiac death (10). The risk of developing ventricular tachycardia increases especially if the prolongation of the QT interval is simultaneously affected by other drugs or there is an inherited disease that primarily prolongs the QT interval, the risk also increases in the case of hypokalemia and bradycardia (11). Some drugs as listed at https://crediblemeds.org, especially antibiotics and antimycotics can prolong the QT interval and may contribute to the development of TdP, similar effect cannot be excluded with newly introduced antiviral drugs.

The main aim of this study was to assess the side effects of a triple antiviral combination on the QTc interval prolongation and to find patients who are at an increased risk of developing malignant ventricular tachyarrhythmias.

MATERIALS AND METHODS

TRIAL DESIGN

We conducted a single-center retrospective trial to evaluate the safety of the three antiviral drugs used in treating patients with previously diagnosed hepatitis C. Initiation of the treatment and combination of antiviral drugs were indicated by an infectious disease specialist according to established guidelines, a control group of patients treated with a placebo was not added. The study conformed to the ethical standard set out by the Declaration of Helsinki. The primary objective of our study was to look into the prolongation of the QTc interval, as a result of the triple combination of antiviral drugs, and the possible development of ventricular tachyarrhythmias. Secondary objectives included determining the PQ and QRS interval and the evaluation of new ECG changes as result of the potential cardiotoxic effects of the antivirals.

PATIENTS AND TREATMENT REGIMES

Antiviral therapy was started in patients with a confirmed diagnosis of hepatitis C in the replication phase. All patients had an established genotype, and we included patients who had not yet been treated with antivirals or who had failed with previous antiviral treatment. Patients were administered with pegylated interferon alfa-2a at a dose of 180 micrograms subcutaneously once a week, and ribavirin at a dose of 1000 mg or 1200 mg daily. The third drug given in the triple combination regimen varied with three possibilities with telaprevir at a dose of 750 mg three times daily or boceprevir at a dose of 800 mg three times daily or simeprevir at a dose of 150 mg once daily. During treatment the patients underwent regular outpatient check-ups with monitoring of the HCV RNA levels in the blood, as well as mineral levels, blood count and liver tests and abdominal ultrasound exams. By default, the therapy was terminated after 24 weeks, with a good treatment effect and with an undetectable level of HCV RNA in the blood, the treatment was terminated earlier.

ECG MEASUREMENT AND ASSESSMENT

Standard 12-leads ECGs were recorded in each patient who was enrolled in our study under the standard conditions in an ECG lab during the outpatient check-ups and were submitted to the hospital database. Any newly detected pathology on the 12 lead ECG was discussed with a specialist in internal medicine. We evaluated the ECG recordings before the initiation of triple combination antiviral drugs, then at 3±1 and 6±1 months after starting treatment. After the patients ended their treatments, the ECG recordings were digitally collected and evaluated with the ImageJ program, which was recommended as a program suitable for processing graphic images by the Nature Methods journal (12). ImageJ makes it possible to evaluate the time duration of the individual ECG intervals with an accuracy of up to a tenth of a millisecond. The QTc interval was measured in three leads (lead II, V1 and V5) in three consecutive cardiac cycles. The longest QTc interval obtained from each beat was then averaged and used for the subsequent evaluation. The end of the T wave was considered as being the contact point with the isoelectric line or if the end of the T wave was unclear, we considered the end as the contact point of isoelectric line in tangent to the steepest part of the descending limb of the T wave. Concerning the RR interval, we considered the variability between the QRS complexes during the previous and current cycle. In the case of atrial fibrillation, the measurement was performed three times and the average of the measurements was chosen as the resulting RR and QT interval. The Bazett and Fridericia formulas were chosen to calculate QTc interval (Fig. 1). Other ECG parameters were also evaluated: the length of the PR

interval and the QRS complex, and any changes throughout the ECG during the treatment were searched for.

$$\mathrm{QTcB} = \frac{QT}{\sqrt{\mathrm{RR}}} \qquad \mathrm{QTcFri} = \frac{QT}{\sqrt[3]{RR}}$$

Fig. 1 Corrected QT interval according to Bazett formula – QTcB. Corrected QT interval according to Fridericia formula – QTcFri.

STATISTICAL ANALYSIS

After the creation of the patient database, the data were statistically processed. Demographic data are reported as mean and standard deviation. We compared the differences between the ECG before the initiation of treatment with the ECG taken after three and six months, respectively. Due to the negative normality test, we used the non-parametric paired Wilcoxon test. A p value < 0.05 is considered as being statistically significant.

RESULTS

DEMOGRAPHIC DATA AND FOLLOW-UP

A total of 23 patients with confirmed hepatitis C in the replication phase who underwent treatment with triple combination antiviral drugs between October 2012 and April 2016 were included in the study. The average age of the patient group was 45 ± 10 years, and 15 (65%) were predominantly male. Genotype 1b was determined in 22 patients, genotype 1a was present only in one patient. In addition, one patient was found to have hepatitis B at that time. The most administered NS3/4A protease inhibitor was telaprevir, which was used in 14 (61%) patients, boceprevir and simeprevir were administered in 3 (13%) and 6 (26%) patients, respectively. The study is consisted of a relatively healthy group of patients. Arterial hypertension was the most common comorbidity, which was present in 5 individuals; type 2 diabetes mellitus, atrial fibrillation, and bronchial asthma were each present separately among three patients in the study. Heart failure and history of myocardial infarction were not detected in any of the patients (Table 1).

Tab. 1 Characteristics of the patients at baseline.

Characteristic	Number	Percentage
Age (years)	45 ± 10	
Female sex	8	35%
Hepatitis C virus genotype 1a	1	4%
Hepatitis C virus genotype 1b	22	96%
Telaprevir	14	61%
Boceprevir	3	13%
Simeprevir	6	26%
Arterial hypertension	5	22%
Diabetes mellitus type 2	1	4%
Atrial fibrillation	1	4%
History of heart failure or myocardial infarction	0	0%
Bronchial asthma	1	4%
Concomitant Hepatitis B	1	4%

PRIMARY OUTCOMES

Before the initiation of treatment with the triple combination of antiviral drugs, the QTc interval according to the Bazett formula was 412 ± 35 ms and the QTc length according to the Fridericia formula was 403 ± 20 ms. During the observed period, there was no statistically significant prolongation of the QTc interval after 3 months and the corrected QT interval according to the Bazett formula (QTcB) = 412 ± 33 ms, p = 0.99; QTcFri = 401 ± 31 ms, p = 0.71. A prolongation of the QTc interval against the initial values was not observed even after 6 months of treatment, QTcB = 405 ± 28 ms, p = 0.87; QTcFri 401 ± 23 ms, p = 0.84 (Fig. 2 and Fig. 3). A treatment-related prolongation of the QTc interval above 450 ms was noted in 1 (4%) patient. No patients had had any polymorphic ventricular tachycardias or any other ventricular arrhythmias or sudden cardiac deaths during the follow-up examinations. None of the patients developed any symptoms of cardiovascular disease. During the follow-up period, 2 patients were using medications which are known to prolong the QT interval and those were indapamide and sertraline.

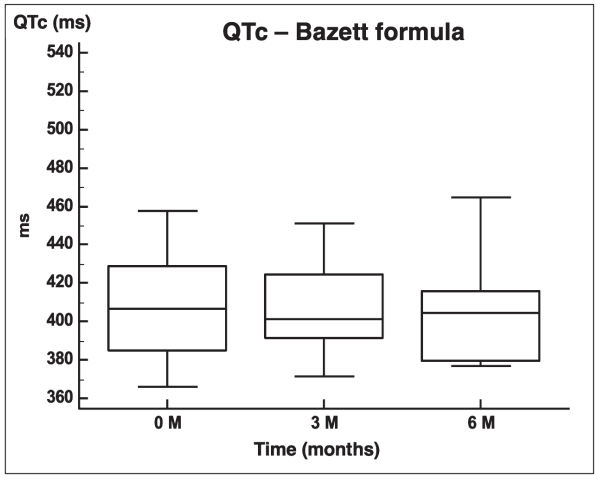

Fig. 2 Length of the QTc interval according to Bazett formula for 6 months follow-up. The middle line of the box plot indicates mean, the upper and lower line of the box plot indicate standard deviation, and the end lines indicate 10th and 90th percentiles.
QTc = corrected QT interval, ms = milliseconds.

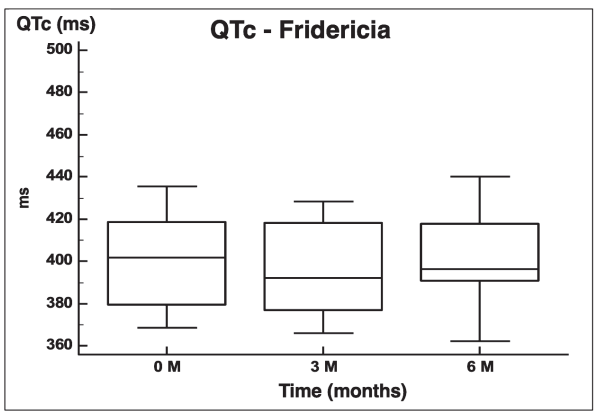

Fig. 3 Length of the QTc interval according to Fridericia formula for 6 months follow-up. The middle line of the box plot indicates mean, the upper and lower line of the box plot indicate mean standard deviation, and the end lines indicate 10th and 90th percentiles.
QTc = corrected QT interval, ms = milliseconds.

SECONDARY OUTCOMES

During the observed period, no statistically significant changes in heart rate were recorded.

Initially it was 69 ± 12 beats per minute (bmp), then after 3 months it was 72 ± 11 bpm, p = 0.29; and after 6 months it was 64 ± 12 bpm, p = 0.84. The PQ interval remained statistically unchanged throughout the follow-up period at 171 ± 21 ms, 178 ± 22 ms, p = 0.20; 174 ± 11 ms, p = 0.38; and the QRS interval did not differ significantly at 106 ± 19 ms, 102 ± 24 ms, p = 0.29; 100 ± 14 ms, p = 0.21 (Table 2). The prolongation of the PQ interval above 200 ms was detected in one patient, but it was not clinically symptomatic, and no syncope or signs of heart failure were recorded. Atrial fibrillation was present in one patient and persisted throughout the study period. An asymptomatic occurrence of left bundle branch block was noted in one patient without any progression of ventricular conduction during the follow-up examination. Even before the initiation of the treatment, incomplete right bundle branch block was detected in 3 patients, left anterior hemiblock in 1 patient, incomplete right bundle branch block and left anterior hemiblock were simultaneously present in one patient throughout treatment (Table 3). No significant changes in the ST segments and T waves were recorded during the monitored period.

DISCUSSION

In this population of patients, treatment with a triple combination of antiviral drugs – pegylated interferon alfa, ribavirin and an NS3/4A protease inhibitor – was not found to significantly prolong the QTc interval and did not cause any significant pathological changes on the ECG. A QTc interval prolongation over 450 ms was detected in one patient, which can increase the risk of developing TdP. However, during the observed period, malignant ventricular tachyarrhythmias were not documented in any patient, nor were their clinical symptoms detected such as syncope, palpitations, or sudden cardiac death.

None of the patients developed any signs of heart failure and there were no statistically significant prolongations of the PQ and QRS intervals, yet one patient had a PQ interval longer than 200 ms at the end of the study period, which was asymptomatic. According to the results of our study, we consider treatment with a triple combination of antiviral drugs to be safe and patients undergoing this treatment are not at risk of developing heart disease as an undesirable side effect.

Tab. 2 Secondary ECG parameters during treatment. bpm = beats per minute, ms = milliseconds.

ECG parameter	Before treatment	3 months after treatment	P value	6 months after treatment	P value
Heart rate (bpm)	69 ± 12	72 ± 11	0.29	64 ± 12	0.84
PQ interval (ms)	171 ± 21	178 ± 22	0.20	174 ± 11	0.38
QRS complex (ms)	106 ± 19	102 ± 24	0.29	100 ± 14	0.21
QT interval (ms)	386 ± 32	381 ± 38	0.31	393 ± 30	0.33

Tab. 3 Persisted ECG findings during follow-up. LBBB = left bundle branch block, iRBBB = incomplete right bundle branch block, LAH = left anterior hemiblock.

ECG findings	Number of patients	Percentage
Atrial fibrillation	1	4%
LBBB	1	4%
iRBBB	3	13%
LAH	1	4%
iRBBB + LAH	1	4%

TREATMENT SUCCESS

The HCV RNA was detected in all patients before starting treatment. Ten patients underwent previously unsuccessful antiviral treatment with a double combination of antivirals (interferon alfa and ribavirin). Treatment with a triple combination of antivirals was successful in 16 patients who did not have detectable viral RNA in their blood at the end of the monitored period. Eight patients had elevated aminotransferase levels before treatment and 4 of them regained normal aminotransferase levels during treatment.

SIDE EFFECTS OF THE TRIPLE THERAPY REGIMES

Successful treatment of HCV infection has undeniable long-term benefits with respect to reducing morbidity and mortality, and the virological response have been recently increased by the introduction of DAAs to the antiviral treatment regimens. The most common side effects with boceprevir are anemia, neutropenia and dysgeusia (altered taste sensation). The most common side effects of telaprevir include anemia, rash, pruritus, and anorectal discomfort (13). Other common side effects of telaprevir treatment include skin toxicity, most often manifesting as eczematous lesions or nonscaling macular lesions. Most toxoallergic exanthems after telaprevir treatment resolve with corticosteroids, but some are refractory to this treatment and the discontinuation of antiviral treatment is therefore something to be considered (14). Another study in patients with an advanced stage of hepatitis C infection and simultaneously diagnosed liver cirrhosis, showed relatively frequent side effects in up to 50% of patients, which led to the worsening of liver function, severe infections, and 2% of the patients died during the study period (15). The first generation DAAs boceprevir and telaprevir, are being replaced by second generation DAAs, such as simeprevir, which lead to higher rates of virologic response, are better tolerated and have lower pill burden,

but are very costly (16). In simeprevir, a second generation AAD, the side effects were generally mild, with mainly headaches, fatigue, and nausea. Only 2% of the patients presented with serious adverse events (2). It is known from the literature that the most common side effects of DAAs are hematological, skin exanthemas and problems with the gastrointestinal tract. So far, only a few clinical cases have been documented with dilated cardiomyopathy, cardiac conduction system disturbances and pericarditis with the combination of pegylated interferon alpha and ribavirin (3–5). There have not been any published cases of significant damage to the cardiovascular system following the addition of DAAs to the standard dual combination antivirals. In addition, no major cardiac events, electrocardiographic or echocardiographic changes were recorded among patients treated with DAAs during regular follow-up (17). In our study, we were not able to confirm any cardiotoxic effects of the triple combination antivirals, and we can consider them safe for the cardiovascular system. However, the drug–drug interactions constitute another concern.

Boceprevir and telaprevir are metabolized by Cyp3A pathway and both molecules are inhibitors of Cyp3A4. Therefore, DAAs are involved in the metabolism of many drugs and, when used simultaneously, the levels of boceprevir and telaprevir may be increased, or their use may elevate the serum levels of other drugs. Interactions should therefore be checked when prescribing DAAs, and increased attention is required especially with drugs such as statins, antidepressants, anticonvulsants, analgesics, and sedatives (13). However, the patients included in the study did not receive the mentioned medication. Their chronic medication was checked, if it was affected by the antiviral treatment, but no interactions were found. Therefore, the levels of administered drugs were not routinely determined.

QTC INTERVAL PROLONGATION AND MEASUREMENT

The QT interval approximates the time interval between the start of depolarization and the end of repolarization of the ventricular myocardium. Drug induced prolongation of the QT interval is associated with an increased risk for ventricular arrhythmias such as TdP and may lead to sudden cardiac death. The association between treatment related QT interval prolongation and proarrhythmic cardiac toxicity has been repeatedly reported and therefore the assessment of QT interval prolongation, has become an integral part of preclinical and clinical drug studies (18). However, a standardized assessment of QT prolongation is still problematic. First, there is a major problem with measuring due to the morphological abnormalities of the T wave. The QT interval could be measured from the beginning of the Q wave until the T wave returns to the baseline or by a tangent inserted to the steepest slope of the downward part of the T wave and the baseline, which provides less inter-reader variability (19). Second, lead II is preferred for measurement because it has the longest QT interval among all leads, but unfortunately, it is present only in approximately 60% of the normal ECGs. Therefore, it is recommended to measure the QT interval in at least 6 leads (3 limb leads and 3 chest leads) and to take the median duration in case of a healthy heart and a similar approach should be applied for patients with heart disease – heart failure, cardiomyopathy, ischemic heart disease, etc. Nevertheless, in other individuals and especially in cardiac patients, it might be safer to replace the median duration by the maximum QT interval (20, 21). In addition, the duration of the QT interval can vary from beat to beat. For this reason, multiple beats (from 3 to 5) should be measured in each ECG lead and averaged, then a median from six or more leads should be taken. Third, the length of the QT interval varies depending on the heart rate; therefore, the corrected QT interval is calculated according to a formula that takes the heart rate into account. The Bazett formula is the most used in clinical practice; however, it unfortunately leads to overcorrection at high rates and under correction at lower rates (11). The relationship between QT and heart rate has been shown to be stable across individuals, but interindividual variation occurs throughout the population. Therefore, individual heart rate correction seems to be the most advantageous, but this requires a previous series of ECGs with different heart rates, which are not usually available in clinical practice (22).

When comparing available formulae, Fridericia and Framingham showed the best heart rate corrections and a significantly improved prediction of the 30-day and 1-year mortalities and thus have the potential to replace the Bazett formula in the standard clinical evaluation of the QTc interval (11). Fourth, an accurate reference interval should include all healthy individuals and identify individuals who are at increased risk of malignant ventricular tachycardias. As an upper limit of normal was set for the QTc interval at 450 ms for men and 470 ms for women (20). However, the Bazett formula leads to an overestimation of patients with a prolonged QTc interval and a reported upper limit of normal should be longer in this formula; 470 ms for men and 480 ms for women respectively, so as to avoid an unnecessary withholding of first line treatment due to a false interpretation of the QTc interval. The lower limit of normal is determined as 350 ms for both men and women and is set for all QTc formulae (11).

CONCLUSION

The study demonstrates that treatment with a triple combination of antiviral drugs: pegylated interferon alfa, ribavirin and an NS3/4A protease inhibitor can be considered as being safe regarding cardiotoxicity and the patients are not at risk of developing any polymorphic ventricular arrhythmias and heart failure as potential side effects of the treatment.

ABBREVIATIONS

bmp = beats per minute, DAAs = direct acting antivirals, HCV = Hepatitis C virus, QTc interval = corrected QT interval, QTcB interval = corrected QT interval according to the Bazett formula, TdP = Torsades de Pointes

AUTHOR CONTRIBUTIONS

JS: manuscript writing, ECG evaluations; RP: manuscript revision, ECG evaluations; MF, FV: manuscript preparation; SP: patients follow-up and management of the treatment; PP: manuscript revision.

CONFLICT OF INTEREST

The authors declare no conflicts of interest in relation to this article.

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BRIEF SUMMARY

This study focuses on the evaluation of ECG changes in patients undergoing hepatitis C treatment with a triple combination of antiviral drugs – interferon alpha, ribavirin, and an NS3/4A protease inhibitor. During the 6-month follow-up, treatment was not found to prolong the QTc interval and not cause any severe pathological changes on the ECG's. The principles of measuring the QTc interval are further described in the study.

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Comparison of Short and Long-Term Results after Injection Laryngoplasty with Radiesse® Voice and Thyroplasty Type I in Unilateral Vocal Fold Palsy

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ABSTRACT

Objectives: Unilateral vocal fold palsy independently of etiology results in glottic insufficiency leading to unfavorable short or long-term impact on voice quality. Our aim was to evaluate the effect of injection laryngoplasty using Radiesse® Voice and thyroplasty type I on glottic closure, voice quality and aerodynamics by comparing preoperative, short- and long-term results.

Materials and Methods: Data of 32 consent patients were reviewed between 2012 and 2023. All patients underwent either injection laryngoplasty (14 patients) or thyroplasty type I (18 patients) under local anesthesia. Maximum phonation time, glottic closure based on videolaryngostroboscopy, VHI-30 values and GRBAS scale were recorded prior, short-term (3 month) and long-term (12 months) after procedures for statistical comparison. Friedman test, Mann-Whitney test and Wilcoxon signed rank tests were used for statistical analysis.

Results: In injection laryngoplasty group, we found significant improvement in maximum phonation time ($p = 0.002$), grade of hoarseness ($p = 0.002$) and breathiness ($p = 0.000$) when comparing results before and short-term after procedure. In thyroplasty type I group we saw significant improvement of maximum phonation time ($p = 0.000$), glottic insufficiency ($p = 0.000$), all three VHI-30 components ($p = 0.000$), as well as grade of hoarseness, breathiness (both $p = 0.000$) and roughness ($p = 0.011$) of GRBAS scale when comparing voice outcome before and short-term after procedure. There was no significant difference in voice outcome results neither between short and long-term results nor between the two groups in any parameter.

Conclusion: These results demonstrate both short and long-term efficiency of injection laryngoplasty and thyroplasty type I in the improvement of voice quality and glottic closure.

KEYWORDS

glottic closure; injection laryngoplasty; thyroplasty type I; unilateral vocal fold palsy; voice quality

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INTRODUCTION

Unilateral vocal cord palsy (UVFP) refers to the reduced motion of the vocal fold on one side due to the hypofunction of the recurrent laryngeal nerve (RLN) or the vagal nerve (VN). Motion disturbance can range from incomplete to complete paresis (also known as paralysis), depending on the altered innervation of the vocal, abductor and adductor muscles. In the clinical practice, the term UVFP is used for both conditions for the sake of simplicity. Most common etiology is iatrogenic injury of the RLN during thyroid gland surgery. Further iatrogenic injury of the nerve can occur due to parathyroidectomy, anterior cervical disc surgery, esophagectomy, thymectomy, neck dissection, carotid endarterectomy, mediastinoscopy and cardiothoracic surgery. UVFP can also develop due to the involvement of the RLN or VN by mediastinal space occupying processes, esophageal, thyroid gland cancer as well as lateral skull base and brainstem lesions. Viral and idiopathic palsies also can occur. UVFP can be asymptomatic or present with various changes in quality of voice due to inadequate glottic closure, swallowing difficulty or even penetration/aspiration which can lead to recurrent pneumonias or life-threatening suffocation. Nerve regeneration depends on the type of neuronal injury (1) and site (2). Spontaneous recovery of the nerve can be expected within the first 12 months (3). Workup in cases of UVFP involves taking a thorough medical history to consider all etiologic possibilities, physical examination with videostroboscopy and evaluation of quality of voice which includes four different approaches: perceptual evaluation (GRBAS scale), acoustics, aerodynamics and subjective rating by the patient (4). If etiology is unknown, further examinations are necessary including most importantly imaging studies (CT or MRI) and viral serology. Additional examinations such as barium swallow test, fibre-optic endoscopic evaluation of swallowing (FEES) and laryngeal EMG may also have their role in the diagnostics. Treatment strategies to improve glottic closure may include speech therapy, injection laryngoplasty (IL), thyroplasty type I (TPL) and reinnervation (5, 6). IL is a safe option, does not interfere with spontaneous recovery and can be repeated if necessary (7). This procedure can be performed under local or general anesthesia with various injectable materials including Gelfoam™, collagen, hyaluronic acid, calcium-hydroxyapatite (8, 9). TPL procedure is a definitive management performed under local or general anesthesia, resulting in permanent change in the position of the vocal fold (medialization) (10–12). This type of framework surgery is performed as a definitive solution for permanent UVFPs. A window is created via external approach on the thyroid cartilage at the level of the vocal fold and an implant (e.g autologous cartilage, hand-carved silastic bloc, Gore-Tex® material or the dedicated Montgomery® thyroplasty Implant System) (13, 14) is placed into this window. Both IL and TPL have the advantage of prompt judgement of voice intraoperatively allowing further correction if necessary. Both voice rehabilitation options are widely accepted and considered safe and effective (7, 15–20). The aim of this study was to evaluate the effect of IL using Radiesse® Voice and TPL and on glottic closure, quality of voice and aerodynamics by comparing preoperative, short- and long-term results in UVFP.

MATERIALS AND METHODS

This study was designed as a prospective study including patients with UVCP treated at the Department of Otorhinolaryngology and Head and Neck Surgery University Hospital Hradec Kralove, Charles University, Faculty of Medicine in Hradec Králové from January 2012 to January 2023. Thirty-two consent patients (18 males, 14 females, average age: 58 years) with UVFP were included regardless of underlying etiology of UVFP, age and gender. We were focusing on two groups of patients: 14 patients prior and after (short and long-term) IL with calcium hydroxyapatite (Radiesse® Voice) and 18 patients prior and after (short and long-term) TPL due to UVFP. We set 3–6 months postoperatively as a short-term result and 1 year after procedure as a long-term result. Indication for type of procedure included period post UVFP and width of glottal insufficiency. Patients whose UVFP lasted more than 1 year or the width of glottic gap was more than 3 mm were treated with TPL. Patients with early diagnosis of UVFP or small glottic gap (less than 3 mm) were treated with IL with Radiesse® Voice. All the 32 procedures were performed under local anesthesia by the same surgeons (V.C., J.D., J.M., K.S.) The following basic parameters were evaluated pre- and postoperatively by three experienced phoniatricians (J.D., J.K.): aerodynamics (maximum phonation time – MPT), changes in glottic gap size (0 – no glottic gap, 1 – small/moderate glottic gap, 2 – large glottic gap) based on videolaryngostroboscopy, self-evaluation of voice quality by the patient (VHI-30) and perceptual characteristics of voice (GRBAS scale – G-grade, R-roughness, B-breathiness, A-asthenia, S-strain). Friedman, Mann-Whitney and Wilcoxon signed-rank tests were used for statistical analysis of the gained data. SPSS Statistics 25.0 software was applied for this purpose (IBM). Level of significance was determined as $p < 0.05$. Ethical Committee of University Hospital Hradec Králové approved the study (number: 201312S03P).

RESULTS

MPT showed significant improvement in both IL and TPL group before and short-term after procedures ($p = 0.001$ and $p = 0.000$ respectively). There was no significant difference between short and long-term results within both groups regarding MPT. Furthermore, significant change was found in glottic closure before and short-term after TPL ($p = 0.000$). However, there was no significant change in glottic insufficiency in IL group ($p = 0.267$) when comparing findings before and short-term after procedure. We found no significant difference between short and long-term results in any groups concerning glottic insufficiency. When we looked at VHI-30 results there was significant improvement in both the functional (F), emotional (E) and physical (P) components of the measure in TPL group before and short-term following surgery (F, E, P – $p = 0.001$). In IL group improvement was noted when comparing

Tab. 1 Statistical results of the injection laryngoplasty group.

	MPTs short-term – MPTs before	MPTs long-term – MPTs short-term	G short-term – G before	G long-term – G short-term
Z	–2.238	–1.320	–2.859	–0.274
p values	0.025	0.187	0.004	0.784
	B short term – B before	B long-term – B short-term		
Z	–3.108	–0.287		
p values	0.002	0.774		

Tab. 2 Statistical results of the thyroplasty type I group.

	MPTs short-term – MPT s before	MPTs long-term – MPTs short term	VHI F% short-term – VHI F% before	VHI F% long-term – VHI F% short-term
Z	–3.295	–0.052	–3.576	–0.283
p values	0.001	0.959	0.000	0.777

	VHI E% short-term – VHI E% before	VHI E% long-term – VHI E% short-term	VHI P% short-term – VHI P% before	VHI P% long-term – VHI P% short-term
Z	–3.101	–0.628	–3.294	–0.026
p values	0.002	0.530	0.001	0.979

	Glottic gap short-term – glottic gap before	Glottic gap long-term – glottic gap short-term	G short-term – G before	G long-term – G short-term
Z	–2.697	–1.342	–3.447	–0.962
p values	0.007	0.180	0.001	0.336

	R short-term – R before	R long-term – R short-term	B short-term – B before	B long-term – B short-term
Z	–2.858	–0.966	–3.541	–0.647
p values	0.004	0.334	0.000	0.518

preoperative and short-term postoperative VHI-30 results (F – p = 0.089, E – p = 0.219, P – p = 0.232) but it was not statistically significant. Analysis of GRBAS scale showed differences between the two groups when comparing before and short-term postoperative measurements. In IL group, there was significant improvement in grade (p = 0.002) and breathiness (p = 0.000). Non-significant improvement was noted in roughness (p = 0.109), asthenia (p = 0.140) and strain (p = 0.311). In TPL group we found significant improvement in grade (p = 0.000), roughness (p = 0.011) and breathiness (p = 0.000). No significant improvement was seen in asthenia (p = 0.206) and strain (p = 0.368). There was no significant difference in any groups when comparing short and long-term GRBAS results. No statistically significant difference was found in results between IL and TPL groups when we compared each parameter. Statistical results are demonstrated in Table 1 and 2. No intraoperative or postoperative complications occurred in connection with the procedures.

DISCUSSION

UVFP independently of etiology may result in low quality of life due to voice deterioration, inefficient cough, swallow difficulties and consecutive penetration/aspiration risk with recurrent pneumonias. Therefore, voice and swallow rehabilitation should equally be granted. Rehabilitation possibilities range from speech therapy to surgery: IL, TPL and reinnervation techniques. Common feature of the listed options is that all of them aims the improvement of glottic closure. Speech therapy is an important supplementary element of the other therapeutic possibilities, though it is employed as monotherapy in the first 12 months while spontaneous recovery can be expected. IL is one of the most frequently applied voice rehabilitation techniques. A wide variety of materials are available as injectable materials. Contrary to the initially used materials (e.g. Teflon, collagen), the currently applied materials cause less foreign body and allergic reactions owing to their tissue-friendly characteristics. Injection of autologous fat tissue is mostly applied under general anesthesia but used as a definitive solution for permanent UVFPs. In acute case, injection of absorbable materials is preferred that do not interfere a possible spontaneous recovery. Injection of cross-linked hyaluronic acid derivatives and polyacrylamide hydrogel (7–9, 21) serves on one hand as early rehabilitation and on the other hand as a trial before permanent surgery, if needed. Calcium hydroxyapatite (e.g. Radiesse® Voice, Renú® Voice) offers a longer lasting (5–18 month) effect (22) placing this material between fast absorbable hyaluronic acid derivatives and definitive solutions including lipoaugmentation and laryngeal framework surgery. IL performed under local anesthesia (also called office-based IL) is a cost-efficient and safe minimally-invasive procedure independently of the used injectable material (23–25). Office-based IL can be applied successfully in case of small glottic gaps (< 2 mm) and acute UVFPs (26), as we also followed this principle when we injected Radiesse® Voice. TPL as a type of laryngeal framework surgery can be performed safely in case of permanent UVFPs, wide glottic closure defects and serious symptoms including inefficient cough, swallow and penetration/aspiration with or without pneumonia (12). In our study we also indicated TPL in case of permanent cases with large glottic insufficiencies (> 2–3 mm) according to the general practice seeing that only expert opinions exist determining glottic gap width for indication of TPL (27).

Success of UVFP rehabilitation – as well as the efficiency of phonosurgical interventions – can be measured in several parameters proposed by the European Laryngological Society (28) and Mattei et al (29). In our study we evaluated

changes in MPT, glottic insufficiency, VHI-30 and GRBAS. We found significant MPT elongation in both IL and TPL group short-term following procedures (p = 0.002 and p = 0.000 respectively) in comparison with preoperative measurements. At the same time no further MPT changes could be recorded in any groups when short and long-term results were compared. Overall, these results show the effectiveness of both procedures and support the aim of both surgical techniques to achieve and maintain proper glottic closure. When glottic insufficiency was evaluated during videostroboscopy, significant improvement could be observed in glottic closure before and short-term after TPL (p = 0.000). However, there was improvement regarding glottic insufficiency in IL group but interestingly it did not prove to be significant (p = 0.267) when comparing findings before and short-term after procedure. We found no significant difference between short and long-term results in any groups concerning glottic insufficiency that may indicate on one hand no migration of the thyroplasty silastic implants during the investigation period and on the other hand it may indicate the expected long-lasting effect of calcium hydroxyapatite owing to its slow absorption.

Functional (F), emotional (E) and physical (P) components of the VHI-30 showed significant improvement in TPL group comparing preoperative and short-term results (F, E, P – p = 0.000). Certain improvement was also noted in IL group when preoperative and short-term postoperative VHI-30 results were compared (F – p = 0.089, E – p = 0.219, P – p = 0.232), although it was not statistically significant. These results highlight improvement of quality of life in both groups.

Regarding GRBAS scale, there was significant improvement in grade (p = 0.002) and breathiness (p = 0.000) in the IL group comparing before and short-term postoperative measurements. Although not significant, but certain improvement was noted in roughness (p = 0.109), asthenia (p = 0.140) and strain (p = 0.311). In TPL group we found significant improvement in grade (p = 0.000), roughness (p = 0.011) and breathiness (p = 0.000). Asthenia (p = 0.206) and strain (p = 0.368) also improved but it did not prove to be significant. No statistically significant difference was found in results between IL and TPL groups when we compared each parameter, which makes the almost identical efficiency of the applied procedures probable. There was no significant difference in any groups when comparing short and long-term GRBAS results suggesting invariable long-term voice quality perceptible by experienced examiner. No minor or major complications occurred neither in the intraoperative nor during the postoperative period in accordance with the literature reporting safety of both IL and TPL (23–25, 30, 31).

For the sake of completeness, we must note the bias of our study. Taking the subjectivity of the examiners' judgement into account when evaluating the glottic gap size is also important. Minimization of this subjectivity could be achieved by comparing pre- and postoperative glottic gap size with more precise software technologies based on for example the estimation of area under the curve. Long-term results were not available in all patients most frequently due to non-compliance regarding follow-up, COVID19 pandemic, other medical health issues and death.

CONCLUSION

Our results suggest that IL and TPL are nearly equally effective procedures in both short and long-term improvement of voice quality and glottic closure in the management of UVFP.

CONFLICT OF INTEREST

The authors declare no competing interests.

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The Role of Frailty Scores to Predict the Outcomes in Non Operative Treatment of Valgus Impacted Neck of Femur Fractures

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ABSTRACT

Objectives: The management of valgus-impacted neck of femur fracture is controversial between operative and conservative treatments. This study aimed to investigate the usefulness of the Clinical frailty Score for predicting the prognosis of patients who underwent non-operative treatment for the valgus-impacted neck of femur fracture (NOF).

Methods: A single-centred retrospective review of patients admitted with valgus impacted NOF. Data were collected from patients' records, including demographics, Clinical Frailty Score (CFS), Nottingham Hip Fracture Score (NHFS) and Abbreviated Mental Test Score (AMTS). Patients were followed up to 24 months postoperatively.

Results: Fifty-eight patients who were treated non-operatively with a mean follow-up of 2.6 years met our inclusion criteria. Twenty-nine patients failed the non-operative treatment and required replacement surgeries, while 29 had successful outcomes (50%). There were no differences between the two groups' mean age and gender distributions (P 0.527 and 0.139, respectively). The successful group had significantly higher CFS (P 0.013), worse AMTS and higher mortality risk based on the NHFS (P 0.006 and P < 0.001, respectively).

Conclusion: This study demonstrates that CFS, AMTS and NHFS can be used as predictors when considering non-operative treatment for the valgus-impacted neck of femur fracture. Patients who are frail, demented and high risk based on the NHFS have higher success rates with non-operative treatment.

KEYWORDS

valgus impacted; neck of femur fracture; non-operative treatment; clinical frailty scale

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INTRODUCTION

The neck of femur (NOF) fracture is one of the most common and devastating injuries encountered by orthopaedic surgeons. The impacted Neck of Femur (NOF) fractures are defined as fractures with close apposition of fragments and various degrees of angulations, according to basic radiographs (1). Because the fracture is commonly impacted laterally and the femoral head trabeculae are tilted in the valgus position, most cases include the femoral head being in this position (1). Impacted fractures represent roughly 15–25% of total NOF fractures (2) and these include Garden 1 and 2 fractures (3, 4), which are classified to be naturally stable (5) according to Beimers et al. (6), who categorised NOF fractures as stable or unstable.

The best course of treatment for impacted NOF fractures is still up for debate, and the research in this field is generally lacking. While some surgeons advocate primary surgical stabilisation, others have found positive outcomes with conservative therapy (7–15). According to reports, the non-operative approach has a success rate of about 85%; however, no published data discusses non-operative treatment indications (10).

Recently, researchers and clinicians have focused on frailty, which is frequently defined as a multifaceted condition in elderly patients, and it has come to be recognised as a determinant in surgical and geriatric outcomes (16). Frailty or ill health may contribute to the explanation of why some elderly individuals recover less than anticipated (17). It is typically caused by a decreased physiological ability to react to stimuli like trauma or infection (18). It means that biological and chronological ages may vary significantly and might be regarded as a loss of physiologic resilience or reserve. Most physicians believe that being weak puts patients in danger, and numerous studies have shown that frailty increases the risk of repeated falls, trips to the emergency room, hospitalisation, higher mortality and institutionalisation in the general geriatric population (19).

Several clinical methods have been scientifically verified to determine a person's frailty. The Clinical Frailty Scale (CFS), which assesses particular areas like comorbidity, function, and cognition to provide a frailty score ranging from 1 (extremely fit) to 9 (terminally ill), is the frailty score that we utilise in our study (20). In general, all prediction issues cannot be resolved by the frailty models now offered by researchers. They do play a significant part in enhancing the quality of patient care by weighing the risks and advantages of various treatment alternatives. Patient recruitment for clinical trials is still an issue to improve outcome prediction. Due to a lack of patient participation, several trials have been prolonged or prematurely discontinued (21–23).

This retrospective cohort study sought to determine the utility of the CFS for predicting the prognosis of patients who underwent non-operative treatment for the valgus impacted neck of femur fracture at our tertiary referral centre, given the prevalence of frailty in patients who sustained proximal femur fractures. We predicted that higher clinical frailty ratings would be linked to higher non-operative therapy failure rates.

This study's primary goal was to assess how the non-operative treatment for impacted NOF fractures performed

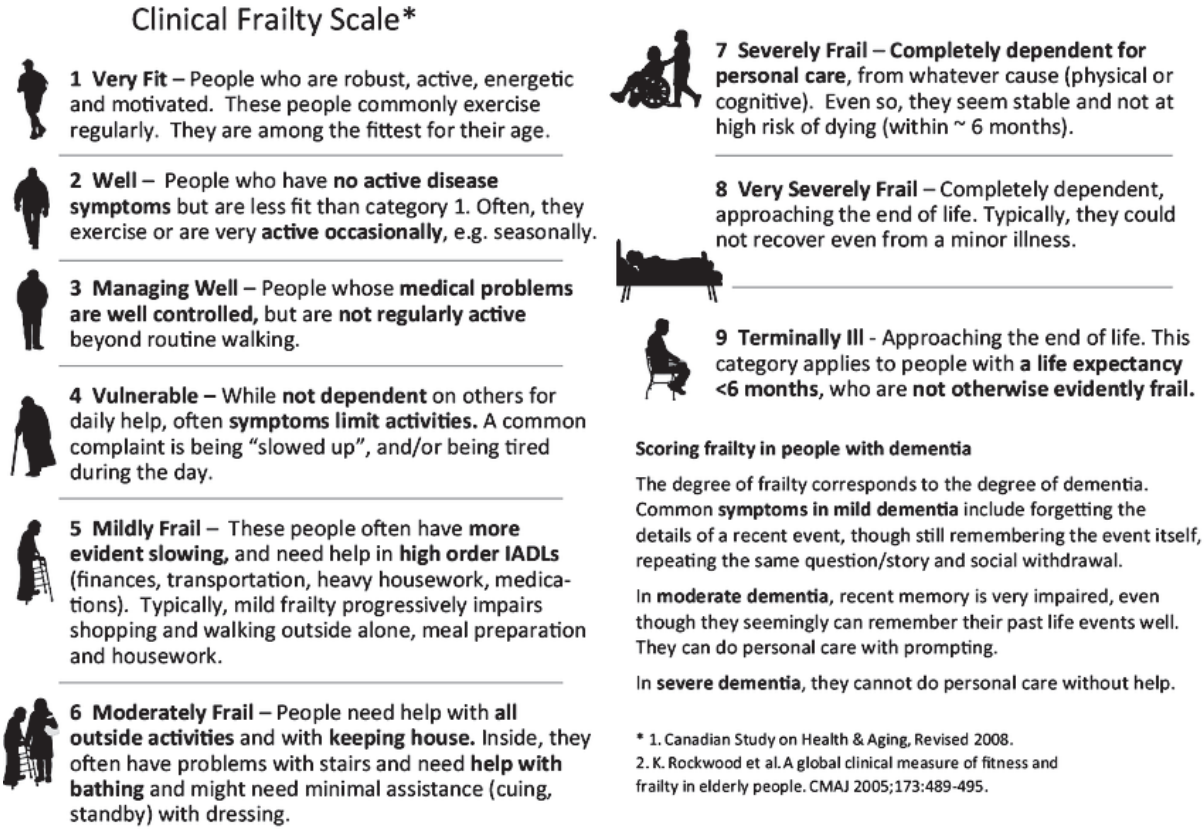

Fig. 1 Table shows the clinical frailty scores.

in connection to frailty score. Evaluation of the impact of age, gender, AMTS, and NHFS on the success of non-operative treatment was the secondary goal.

METHODS

This is a retrospective analysis of prospectively collected data hence ethical approval was not required. The study was carried out in a tertiary centre in the United Kingdom. Patients were initially identified using the Hip Fracture Database between 2016 and 2020. Data were collected from patients' notes, clinical letters and radiological images. We included adult patients with traumatic valgus impacted NOF fractures who were diagnosed based on x-rays or CT scans and treated non-operatively at the first instance. Garden 1 and 2 NOF fractures are regarded as impacted fractures that were considered inherently stable. We followed up patients up to a minimum of nine months post injury. The United States Food and Drug Administration (USFDA) defines a non-union as a fracture at least nine months old and has not shown any signs of healing for three consecutive months. Patients who had no documented follow-up to confirm the success or failure of their treatment were excluded. We collected patients' demographic data, AMTS, NHFS and frailty scores. The orthogeriatric team in our department has adopted the Clinical Frailty Scale (CFS) as a rapid bedside frailty screening tool. Based on this scale, patients are classified as very mild, mild, moderate, severe, very severe frailty and terminally ill (Figure 1).

The Abbreviated Mental Test Score (AMTS), which assesses the patient's memory (24), and the Nottingham Hip Fracture Score (NHFS), which estimates the mortality rate (25), were also reported. According to the AMTS, patients who scored more than six were classified as coherent and six or less were classified as demented. NHFS was used to estimate mortality rates and based on this; patients were classified as low (NHFS ≤ 4) or high risk (NHFS > 4). The Nottingham Hip Fracture Score (NHFS) is a scoring system that predicts 30-day mortality for patients after hip fracture.7 It is made up of seven indices. Pendent predictors of 30-day postoperative mortality that have been incorporated into a risk score: age (66–85 and ≥86 years); sex (male); number of co-morbidities (≥2), admission mini-mental test score (≤6 out of 10), admission haemoglobin concentration (≤10 g dl21), living in an institution; and the presence of malignant disease.

Patients who had fracture displacement, developed non-union or avascular necrosis were considered as failed treatment. While those who healed radiologically and progressed with mobility were considered as successful. We compared those who failed the non-operative treatment with the successful ones to see if any variable affected their outcome. Between-group comparisons of categorical variables were analysed using the Chi-square test for independence. The level of statistical significance was set at a p-value of <0.05. Statistical analysis was performed using SPSS for Windows version 27.0 (IBM Corp., Armonk, New York) and GraphPad Prism 9 software version 9.4.1

RESULTS

We reviewed all patients admitted between 2016 and 2020 with valgus impacted neck of femur fractures and treated non-operatively at first instance. 92 patients were treated non operatively of whom 29 passed away within the first nine months post injury. We excluded those 29 patients, and 5 patients had no documented follow-up. Fifty-eight patients met our inclusion criteria. Twenty-nine of them had successful outcomes following non-operative treatment and equally twenty-nine failed and required an operative intervention such as a total hip replacement or a hemiarthroplasty. The mean age of the successful group was 81.75 years (SD 9.1) including 10 males and 19 females. The failed group had 5 males and 24 females and the mean age was 80.17 years (SD 9.5). there were no statistically significant differences between the two groups' demographics (Table 1). In the successful group, the mean Frailty score was 5.17 (SD 1.57) which is statistically higher than the failed group (Table 2). In addition, the AMTS and the NHFS scores were significantly worse in the successful group (Table 2). According to the CFS we classified patients as frail if they score 6 or more (moderate frailty to terminally ill patients). The number of frail patients was significantly higher in the successful group (P 0.024) (Table 3). According to the AMTS we classified those patients as coherent if they scored 7 or more and demented if scored less than 7. There were significantly more demented patients in the successful group (0.008). The NHFS which estimates patients' mortality risk, was used to subgroup patients to high and low mortality risk. Those patients in the successful group had significantly higher mortality risk than the failed ones (Table 3).

Tab. 1 Compares gender and age between the two groups.

Groups	Male	Female	Age > 85	85 or less
Successful	19	10	9	20
Failed	24	5	9	20
Chi-Square	0.230		1.000	

Tab. 2 Compares the means of the tested variables.

Groups	Age	Gender	Frailty	AMTS	NHFS
Successful	81.75	10 Male	5.17	5.68	5.62
	SD 9.09	19 Female	SD 1.57	SD 3.11	SD 1.18
Failed	80.17	5 Male	4.17	7.86	4.31
	SD 9.5	24 Female	SD 1.31	SD 2.51	SD 1.53
P value	0.527	0.139	0.013	0.006	<0.001

Tab. 3 Compares surgical risk, mental state and frailty between the two groups.

	Surgical risk		Mental state		Frailty	
Groups	low risk	high risk	demented	coherent	non frail	frail
Successful	7	22	21	8	15	14
Failed	15	14	10	19	24	5
Chi-Square	0.057		0.008		0.024	

The successful group had more frail patients compared to the failed group on the other hand those who failed we remarkably less frail (P 0.024). Furthermore, the failed group contained more coherent patients with lower mortality risk (Figure 2).

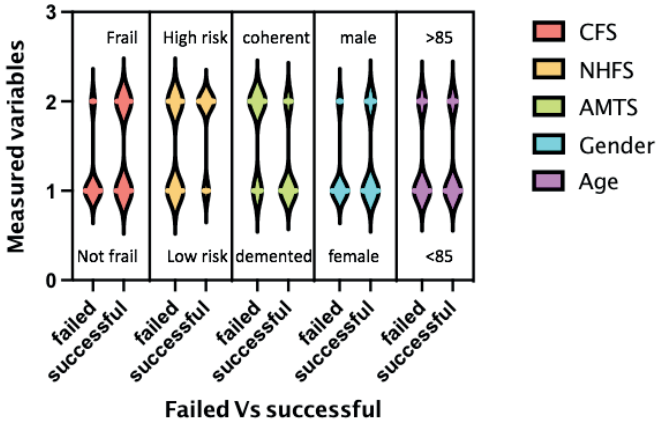

Fig. 2 Plot shows patients' distribution in the measured variables.

DISCUSSION

This paper discusses utilising the CFS, AMTS and NHFS in predicting the outcomes of non-operative treatment of the valgus impacted neck of femur fractures. Patients who were frail, demented and with high surgical mortality risk had satisfactory outcomes following non-operative treatment. On the other hand, treatment failure was more noticed in those who are not frail, coherent and have low surgical risk. To our knowledge, this is the first study in the literature to discuss using CFS, AMTS and NHFS as predictors.

Frail patients who suffer hip fractures can be challenging to manage, necessitating a multidisciplinary approach to patient care. These patients frequently have many medical comorbidities and represent a substantial health burden, which is expected to rise as the population ages and becomes more comorbid (18). Frailty as an independent risk factor for mortality, morbidity, extended length of stay, and readmission rate is not a novel finding; however, with the application of the CFS, all members of the multidisciplinary team, including the surgeon, may now easily apply frailty to hip fractures (26).

In addition, the CFS is a helpful tool for determining the best course of action (i.e. relatively quicker operations with shorter anaesthetic time or hemiarthroplasty over total hip arthroplasty in frail patients). Its usage in the orthopaedics and orthogeriatric treatment models is supported by its simplicity of application and prognostic advice. The CFS reduces age-related bias in surgical management decision-making by identifying independent, non-frail older patients.

The published literature shows controversy on how to treat Impacted Femoral Neck Fractures, and the most effective way to treat an impacted fracture is still up for dispute. While primary surgery is advised by some researchers, such as internal fixation and arthroplasty, others report positive outcomes from conservative measures (1–15). Raaymakers et al. (27) successfully treated 170 affected femoral neck fractures with early mobilisation and weight-bearing in their prospective trial. At one year, mortality overall was 16%. One hundred forty-three fractures (86%) in the 167 patients were monitored until fracture healing or secondary instability. Only individuals over 70 and younger patients with a limited life expectancy experienced instability. Age (above 70 years) and poor general health (determined by stepwise logistic regression analysis) were risk factors. Although the findings of this study support the non-operative treatment, their identified risk factors are in contrast to ours. The recent advances in bedside care and community nursing have hugely impacted the outcomes of managing the elderly population with limited mobility, including those with lower limb fractures. Measures like chest physiotherapy, venous thrombo-embolism prophylactic treatment and bedsores management have generally improved the management outcomes (28–30). These can be considered contributing factors that might explain why our successful cohort differs.

Conservative treatment proponents point out that because most patients would heal without internal fixation when adequately supervised, the risks associated with the operation are not justified in preventing displacement in a tiny fraction of cases (12). Others support using hip arthroplasty to treat elderly patients with non-displaced or impacted NOF fractures to promote early mobility, recovery and lower mortality (13–15, 31). Hemiarthroplasty is thus advised for patients above the age of 75. However, many elderly individuals are not candidates for surgery due to a combination of high-risk comorbidities, and some patients may even decline the procedure. The postoperative death rate is significant in people over 65 having neck of femur surgery (32).

A systematic review by Xu et al. (33) included 29 studies comprising 5071 individuals with undisplaced femoral neck fractures. One thousand one hundred twenty patients were treated nonoperatively, while 3951 were treated surgically. In the former and latter groups, the union rates were, respectively, 68.8% (642/933) and 92.6% (635/686) (p 0.001). Avascular necrosis occurred at an incidence of 10.3% (39/380) in the group receiving conservative care against 7.7% (159/2074) in the group receiving surgical care (p = 0.09). The authors concluded that surgery had a greater union rate and a propensity toward less avascular necrosis.

To our knowledge, no study has considered frailty a predictor of non-operative treatment of valgus impacted neck of femur fracture. Our study has demonstrated the potential prognostic value of the CFS grading tool as a risk stratification index before surgical management of impacted valgus neck of femur fractures. This study has found a significant relationship between the degree of frailty (as defined by the CFS) and the success of non-operative treatment. Furthermore, our study highlighted that patients with dementia and high mortality based on the NHFS are more likely to do well with non-operative treatment. Although there is an association between frailty and dementia but not all demented patients are frail, and not all frail patients have dementia. Based on this study,

predicting poor outcomes after conservative treatment helps inform the treatment decision and communication with patients and their carers.

The limitation of this study includes its retrospective nature, although the data were collected prospectively. Add to that the small number of patients and being a single-centred study.

CONCLUSION

Our study demonstrates that CFS, AMTS and NHFS better predict failure of non-operative treatment of valgus impacted neck of femur fracture. Patients who are frail, demented and have high mortality based on the NHFS have higher success rates with non-operative treatment. Functional treatment of frail patients with impacted femoral neck fractures seems, therefore, to be justified. Further research in this area is required.

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Survival Analysis of Newly Diagnosed Multiple Myeloma Patients after Frontline Autologous Stem Cell Transplantation in a Real-Life Setting

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ABSTRACT

Introduction: Autologous stem cell transplantation (ASCT) is the standard consolidation option for transplant-eligible patients with multiple myeloma (MM). The aim of this study is to report the overall survival (OS) and progression-free survival (PFS) outcomes after frontline ASCT in newly-diagnosed MM (NDMM) patients in a real-world setting.

Methods: We conducted a retrospective, survival analysis of all NDMM patients included in the MM Uruguayan Registry.

Results: We included 151 NDMM patients treated with induction therapy followed by high-dose melphalan and ASCT as consolidation. The median age at diagnosis was 59 years, and the international staging system (ISS) risk groups were ISS-III 32.9%, ISS-II 37.8%, and ISS-I 29.4%. Frontline induction regimens included bortezomib in 61.6% of cases, and maintenance therapy was used in 63.9% of reported cases. With a median follow-up of 42 months, the 36-month OS and PFS for the whole group were 82.4% (95% CI 75.9% to 89.4%) and 63.8% (95% CI 55.6% to 73.3%), respectively, median OS of 98 months and median PFS of 47 months. The 100-month OS and PFS for the entire group were 48.0% (95% CI 34.9% to 66.0%) and 17.3% (95% CI 8.4% to 35.8%), respectively.

Conclusion: ASCT is a feasible, safe, and potent strategy that provides a prolonged median OS and PFS in NDMM patients. This approach can be implemented in low-income countries.

KEYWORDS

multiple myeloma; autologous transplantation; survival analysis; melphalan conditioning

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INTRODUCTION

Multiple myeloma (MM) accounts for 1% of all cancers and 10% of hematologic malignancies, with an incidence of approximately 4/100,000/year (1). In the western world, the incidence of MM varies from 24,280 to 30,330 new cases and 12,650 deaths in 2016, with an age-standardized incidence rate of 5 cases per 100,000 inhabitants (2). In Uruguay, the standardized incidence by age is 2.1 to 3.5 cases per 100,000 inhabitants (3).

Over the last three decades, the introduction of novel drugs has significantly improved the survival rates of MM patients. High-dose therapy (HDT) followed by autologous stem cell transplantation (ASCT) remains the standard consolidation option for newly diagnosed MM (NDMM) patients who are fit, as demonstrated by the randomized phase three Intergroupe Francophone du Myeloma (IFM) 2009 trial, which reported overall survival (OS) of 88% at three years and progression-free survival (PFS) of 61% in the group that received ASCT (4, 5).

Several factors, including comorbidities, disease biology, and type of induction treatment, have been associated with outcomes after ASCT (6).

ASCT is available to all fit MM patients in Uruguay, regardless of their healthcare provider. However, there are limited local publications focusing on the outcomes of transplantation. Our study aims to fill this gap by reporting the overall survival (OS) and progression-free survival (PFS) achieved using high-dose melphalan and ASCT as consolidation therapy in the Uruguayan population.

PATIENTS AND METHODS

We conducted a retrospective survival analysis of all consecutive active newly diagnosed multiple myeloma (NDMM) patients recorded in the Uruguayan MM Registry between 2009 and 2021 who received high-dose melphalan and autologous stem cell transplantation (ASCT) as consolidative therapy. Patients with incomplete information regarding diagnosis, last control date, relapse/progression or death date, smoldering MM, and plasma cell leukemia were excluded. We analyzed parameters allowing International Staging System (ISS) staging and treatment outcomes evaluation, including ASCT outcomes.

Ethics Committees from participating institutions approved this study.

DEFINITIONS

The diagnosis of MM and response to therapy were defined according to the International Myeloma Working Group (IMWG) criteria (7). High-risk MM was defined using the International Staging System (ISS). Revised ISS (R-ISS) was not reported as cytogenetic analyses were not available in the majority of patients treated before 2015. Overall survival (OS) was defined as the time from diagnosis to the date of death or last contact. Progression-free survival (PFS) was defined as the time from the start of non-radiative therapy to the date of progression, relapse, death by any cause, or last date of follow-up. Early relapse was defined as relapse within the first 12 months from diagnosis.

TREATMENT

Induction therapy was selected by the treating physician, according to current guidelines, reimbursement policies, and drug availability. To simplify the analysis, we classified induction protocols into bortezomib-based regimens (BBR) and non-bortezomib-based regimens (NBBR). ASCT was authorized if partial remission (PR) was achieved after frontline therapy. The standard conditioning regimen used in Uruguayan transplantation centers is melphalan 200 mg/m^2. Mortality due to auto-HSCT was defined as death due to any transplantation-related cause other than disease relapse in the first 100 days after transplantation.

STATISTICAL ANALYSIS

We used Statistical Package for Social Sciences (SPSS) v.25 and R for statistical analysis. Descriptive statistics included quantitative and qualitative variables; quantitative variables were represented with median and interquartile range (IQR) or mean and standard deviation, depending on the normality of distribution determined by the Kolmogorov-Smirnov test. Qualitative nominal or ordinal variables were represented as percentages or proportions. To compare quantitative variables, we used nonparametric methods, and the comparison of proportions was performed with the chi-square test. Survival was analyzed using Kaplan-Meier curves and the Log-rank test, with p-values considered statistically significant when <0.05. For multivariate analysis, we used the Cox regression model, including only those variables with a significant impact observed during univariate analysis.

RESULTS

We analyzed a cohort of 151 patients with active NDMM, with a median age at diagnosis of 59.0 years (IQR 11.0, range 31 to 71) and 61.6% being male. The median follow-up for the entire group was 42.0 months (IQR 42.0, range 5 to 147). Most patients had an advanced Durie-Salmon stage III (70.7%). According to ISS risk staging (n = 143), 32.9% were classified as ISS III, 37.8% as ISS II, and 29.4% as ISS I. Median values for hemoglobin, creatinine, calcium, serum monoclonal component, and bone lytic lesions frequency were 10.0 g/dL (IQR 3.4), 1.0 mg/dL (IQR 0.7), 9.4 mg/dL (IQR 1.1), 2.7 g/dL (IQR 3.6), and 77.5%, respectively. At diagnosis, 6% of patients required hemodialysis, but none continued dialysis at the time of ASCT. The majority of patients had IgG MM (56.3%), followed by IgA (26.4%), light chain (15.9%), and non-secretory (1.3%) MM. Table 1 presents further details on the characteristics of the included patients.

Tab. 1 Characteristics of patients included in the study.

	n	%
Total, n (%)	151	100,0
Age		
Age ≥ 60 years	59	44.7
Sex		
Male	93	61.6
Female	58	38.4
MM Subtype		
IgG Kappa	47	31.1
IgG lambda	38	25.2
IgA kappa	28	18.5
IgA lambda	12	7.9
LC	24	15,9
Non-secretory	2	1.3
ISS Stage (N = 143)		
ISS I	36	29.4
ISS II	48	37.8
ISS III	42	32.9
Laboratory at diagnosis		
Hemoglobin < 10 g/dL	76	50.3
Calcium > 11.5 mg/dL	20	13.2
Creatinine > 2 mg/dL	28	18,5
Lytic lesions	117	77.5
Induction régimen		
BBR	93	61.6
Pretransplant response		
≥ VGPR	85	56.3
Post-transplant response (N = 116)		
≥ VGPR	99	85.3
Relapse <12 months from diagnosis.	13	9.1
Maintenance (N = 122)		
Maintenance	78	63.9
No maintenance	44	36.1

DS; Durie-Salmon; ISS, international staging system; VGPR, very good partial response; MM, Multiple myeloma; BBR, bortezomib-based regimen; OS, overall survival.

INDUCTION REGIMEN

Of the patients included in the study, 61.6% received bortezomib as part of their frontline induction regimen. Among bortezomib-based regimens (BBRs), the most common was CyBorD (cyclophosphamide, bortezomib, and dexamethasone) at 43.7%. Other BBRs used included VTD (bortezomib, thalidomide, and dexamethasone) at 7.3%, VRD (bortezomib, lenalidomide, and dexamethasone) at 6.6%, VTD-PACE (VTD-cisplatin, doxorubicin, cyclophosphamide, and etoposide) at 3.3%, and PAD (bortezomib, doxorubicin, and dexamethasone) at 0.7%. Among non-bortezomib-based regimens (NBBRs), the most common was CTD (cyclophosphamide, thalidomide, and dexamethasone) at 28.5%. Other NBBRs used included TD (thalidomide and dexamethasone) at 8.6%, and others at 0.7%.

RESPONSE RATE

At the time of ASCT, all patients met the local criteria for the procedure, resulting in an overall response rate of 100% (≥ PR). Of these patients, 56.3% achieved a very good partial response (VGPR) or better, while 24.5% achieved a complete response (CR). In 116 patients for whom post-ASCT response was reported, 85.3% achieved a VGPR or better and 54.3% achieved a CR. The rate of CR was significantly higher after ASCT compared to that achieved during induction therapy.

MAINTENANCE THERAPY

Maintenance therapy was reported in 122 patients. The type of maintenance was detailed in 78 patients (63.9%): 29.5% Thalidomide, 42.3% Lenalidomide, 17.9% Bortezomib, and 10.3% others. The duration of maintenance was not reported.

SURVIVAL

For the whole group, the 100-month overall survival (OS) and progression-free survival (PFS) were 48.0% (95% CI 34.9% to 66.0%) and 17.3% (95% CI 8.4% to 35.8%), respectively, with a median OS of 98 months (95% CI 63.8 to 132.2) and a median PFS of 47 months (95% CI 39.4 to 54.6) (Figure 1). Additionally, the 36-month OS and PFS were

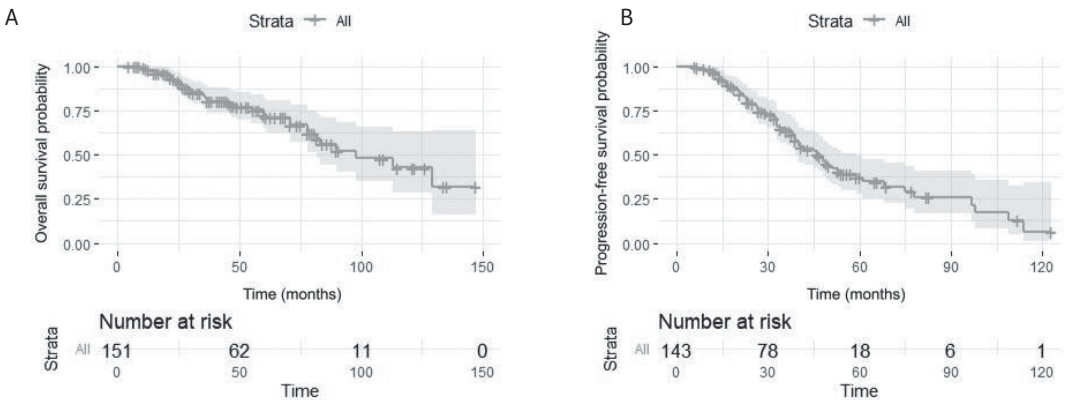

Fig. 1 (A) Kaplan-Meier curve of overall survival for the whole group included; (B) Kaplan-Meier curve of progression-free survival for the whole group included.

82.4% (95% CI 75.9% to 89.4%) and 63.8% (95% CI 55.6% to 73.3%), respectively.

When analyzed by the ISS group, patients with ISS-II/III had a reduced 100-month OS (42.0% (95% CI 26.5% to 66.7%) versus 63.0% (95% CI 41.8% to 94.9%), p = 0.076) and PFS (10.2% (95% CI 3.2% to 32.4%) versus 32.3% (95% CI 12.8% to 81.8%), p = 0.010) compared to ISS-I. However, there were no significant differences in median PFS or OS between patients who achieved ≥VGPR after induction and those who achieved PR (p > 0.05).

Regarding the induction therapy used, the 100-month OS for patients who received BBR or NBBR (46.5% (95% CI 32.5% to 66.7%) versus 47.4% (95% CI 27.6% to 81.4%), respectively; p = 0.03). The PFS was not significantly different between these groups (25.2% (95% CI 11.8% to 54.0%) versus 10.6% (95% CI 2.2% to 50.8%), respectively; p = 0.422).

Patients who suffered early relapse (n = 13) had a reduced median overall survival (24 months, 95% CI not calculated as the last event occurred in the 50th percentile), compared to those with relapse after 12 months from diagnosis (98 months 95% CI 64.5 to 131.5).

DISCUSSION

This analysis presents information on the factors that influence survival in a real-life cohort of transplanted patients with newly diagnosed multiple myeloma (NDMM) in Uruguay. Our findings showed a 36-month overall survival (OS) and progression-free survival (PFS) rate of 85.2% and 62.8%, respectively, for the whole group, which is comparable to the results of three randomized clinical trials (IFM2009, EMN02/HO95, and DETERMINATION) that reported improved PFS and OS rates with the use of high-dose melphalan (HDM) and autologous stem cell transplantation (ASCT) compared to a non-transplant strategy. The median PFS survival in these trials ranged from 50 to 67.5 months, with a 5-year OS rate of approximately 80%. As expected, our results also showed a lower OS rate in NDMM patients with ISS-II/III, which was associated with a reduced OS rate of 42% at 100 months (5, 8, 9).

Our results are in line with those reported by the IMWG, in which in 7291 MM patients, albumin level < 3.5 g/dL (OR = 1.36, p = 0.023) and B2m ≥ 3.5 mg/dL (OR 1.86, p < 0.001) had a negative effect on 10-year OS in NDMM transplant eligible patients (10).

We did not find that the use of BBR therapy significantly improved OS and PFS rates. These results could be explained by national policies, since until 2017 standard-risk patients did not receive bortezomib or lenalidomide, which were only authorized for high-risk patients. In consequence, patients receiving novel drugs had a poorer prognosis and this could explain the results, along with the low number of patients. A similar finding was observed in a Mayo Clinic study, using a risk-adapted therapy approach, in which no difference in OS and PFS was found according to the induction regimen (immunomodulatory drug–proteasome inhibitor combination, proteasome inhibitor–alkylator combination, and a doublet therapy). After adjusting for cytogenetic risk, OS between the 3 classes of regimens remained non-significant (11). However, this differs from the results of the Southwest Oncology Group trial, where the addition of bortezomib to lenalidomide and dexamethasone resulted in a significantly improved PFS and OS.

We observed an improvement in the depth of response in 29% of patients after ASCT, with a significant increase in complete response (CR) rates from 24.5% to 53.3%. Although the difference was not statistically significant, achieving a more profound response was associated with better PFS and OS rates. Frontline ASCT as consolidation therapy remains a viable option for NDMM patients, particularly in countries with limited access to new frontline therapies.

Early relapse was the most impactful predictor for mortality in NDMMM patients receiving ASCT. In our study, we did not find factors for this condition. Several reasons may explain this finding. First, novel cytogenetic risk factors associated with lower PFS were not studied. Recent staging systems have demonstrated the additive effect of cytogenetic aberrancies such as high-risk IgH translocation (t(4;14), t(14;16), and t(14;20)), del17p, 1q gain/amplification, or del1p, on the risk of death or progression by MM (12-14). Additionally, even when these aberrancies are present, there are conditions with higher risk among them, including a clonal fraction higher than 55% for del17p, mutational status of TP53 and t(4;14) with translocation breakpoint located within the NSD2 gen (Not located upstream NSD2 or in the UTR-5) (15–17).

Second, the duration of maintenance was not reported. Third, the number of patients is low. Fourth, patients with severe renal impairment and/or chronic dialysis have not been transplanted.

The main limitations of this study are the low number of patients and the low availability of cytogenetic analyses. No patients with severe renal impairment and/or dialyses were included. This may have limited, or unintentionally biased, the power of some associations.

Another important limitation regarding the comparison between therapeutic regimens is the reduced number of patients included in each group. It would be important to conduct studies with a higher number of patients to corroborate our results.

CONCLUSIONS

Frontline ASCT as consolidative therapy for NDMM is safe and is associated with prolonged OS and PFS. ISS II-III and early MM relapse (within the first 24 months from ASCT) were associated with shorter PFS and OSn NDMM, regardless of induction therapy. In contrast to the limited access to novel drugs, ASCT is widely available in Latin America. This is a feasible, safe, and potent strategy, providing more than 80% 5-year OS.

CONFLICT OF INTEREST

Authors have no conflict of interest to declare. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Gait Disturbance … of Red Herrings, Oranges, and Lemons – A Case of Missed Vitamin C Deficiency and Lessons Learnt

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ABSTRACT

Vitamin C deficiency resulting in scurvy, is considered to be a rare nutritional disorder in developed countries, thus leading to underdiagnosis with exposure to unnecessary investigations and delay in appropriate treatment. The wide myriad of clinical signs and symptoms with which vitamin C deficiency can present (including haematological, musculoskeletal and vague constitutional symptoms that overlap with other common medical conditions), also contributes to this diagnostic challenge. Despite scurvy being habitually thought to be present in children with neurodevelopmental conditions such as autism spectrum disorder, other important at-risk groups that frequently tend to be forgotten include children with persistent fussy eating behaviour, and children with abnormal vitamin C metabolism. We hereunder present a case of a 10-year-old boy who presented to an acute general hospital for further investigation with gait disturbance. The lack of detailed nutritional assessment on presentation in the first instance led to a missed diagnosis of vitamin C deficiency, thus exposing the child to a wide array of unnecessary investigations and treatments. The added perplexity to the case resulting from false positive results of investigations performed as part of this child's workup, is also discussed.

KEYWORDS

Scurvy; ascorbic acid deficiency; pediatrics; nutritional deficiency; child nutrition disorder; nutrition assessment; case report

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INTRODUCTION

Scurvy secondary to vitamin C deficiency is considered to be a rare nutritional disorder in developed countries given the high level of nutrition standard in general. Given the important role that vitamin C holds for skin and soft tissue function including iron absorption, wound healing, and collagen biosynthesis; vitamin C deficiency causes a myriad of clinical signs and symptoms. These include haematological abnormalities, musculoskeletal complaints, and an extensive range of other constitutional symptoms (1, 14, 15). Despite all the latter clinical manifestations, vitamin C deficiency can still be overlooked and challenging to diagnose clinically (2).

Vitamin C deficiency within the paediatric population tends to occur in children with very restrictive diets (3). This group of children includes those with neurodevelopmental disorders, in particular autism spectrum disorders. This tends to be a result of unbalanced nutritional intakes and food selectivity. However, it can also occur in children without clear autism or neurodisability (4). We hereunder present an interesting case of a child presenting with vitamin C deficiency and scurvy, with special emphasis on the importance of considering vitamin C deficiency as part of the differential diagnosis for children presenting with vague constitutional symptoms and gait disturbance. We thereby advocate nutritional and behavioural assessment to be included more routinely as part of clinical paediatric reviews, given the valuable information that these can provide as a clue to the diagnosis, thus avoiding unnecessary investigations.

CASE REPORT

A 10-year-old boy, presented to the paediatric outpatient clinic with a 2-month history of progressively worsening pain in his lower back, bilateral anterior thighs and both knees. As a result of his increasing pain, he eventually also developed an antalgic gait, with difficulty standing up from squatting, and difficulty with walking short distances unaided, requiring a wheelchair to mobilise. Symptoms were reported to be worse towards the end of the day. There was no history of fever, trauma, or recent illness. The child denied urinary or faecal incontinence.

On review, mild rectus femoris atrophy could be observed together with reduced power of grade 4– proximally in both lower limbs and 4+ proximally in the upper limbs using the Medical Research Council (MRC) muscle power scale. Tone, deep tendon reflexes and sensation were normal throughout. Lordotic posturing was noted on standing and mild tenderness could be elicited on the lower back. There were no signs of arthropathy. Gait was observed to be slow, antalgic, narrow based, but not clearly ataxic. There were no cerebellar signs elicited. Romberg sign was negative and cranial nerves were fully intact. Systemic examination was otherwise normal.

Initial blood investigations including a full blood count, inflammatory markers, rheumatology screen and creatine kinase levels were normal. Magnetic resonance imaging (MRI) of the head, spine and thighs was also performed to exclude intracranial, spinal, and demyelinating abnormalities and on initial review these were reported to be normal. Somatic symptom conversion disorder was also discussed as a possibility.

In view of normal initial investigation results, a watch-and-wait approach was initially adopted, with regular physiotherapy input and adequate analgesia cover. Despite this, minimal improvement was seen over the following days. At this point, the mother mentioned a similar episode of gait disturbance and lower limb pain associated with fleeting arthralgias mainly involving the knees, ankles and hip joints, two years earlier at 7 years of age which resolved spontaneously over a few months. The history given by the mother was unclear, but allegedly the episode had been attributed to post streptococcal reactive arthritis and/or viral myositis in view of influenza A being detected on his respiratory screen together with high anti-streptolysin O titre levels on his blood results. A missing part of her history involved the child's history of restricted food intake, mainly consisting of pasta, bread, butter, cereal, milk, water. Review of past investigations performed later during the child's stay in fact revealed that a low Vitamin C level of <1.0 mg/L had been noted, and the child was advised to start vitamin C supplementation, with which he had been uncompliant but was not further followed up given that his symptoms had gradually resolved spontaneously over a few weeks.

Given the child's clinical findings and lack of improvement, nerve conduction studies were performed which excluded large fibre polyneuropathy. Cerebrospinal fluid and serum blood antibody analysis (including anti-acetylcholine receptor antibodies, anti-muscle specific kinase and anti-ganglioside antibodies) revealed positive anti-ganglioside monosialic 2 and GD1b antibody titres. Therefore, despite the clinical picture not being consistent with classical Guillain-Barré syndrome and considering the small possibility of a sensory painful inflammatory polyneuropathy, it was decided to attempt a trial of intravenous immunoglobulin (IVIG) administration, again with only mild improvement noted.

Admission on the ward allowed for the opportunistic observation of the boy's behaviour and dietary eating habits. The child was noted to exhibit elements of anxious behaviour and strict routines. He was also noted by the nursing staff to refuse most food provided, including that prepared by the mum herself. Further in-depth questioning revealed a longstanding history of restrictive eating habits with very minimal intake of fruit and vegetables, which had not been previously highlighted as yet during the clinical reviews performed since his current admission. The mum also confirmed that the child had always had relatively strict behavioural routines and had been noted to become seemingly increasingly anxious during the past year, mainly related to school performance. The child had allegedly already been seen by the child development assessment unit in the past, but no definitive diagnosis had been made yet with regards to his behaviour and development.

Considering this new information, a full nutritional and endocrine screen including iron profile, thyroid functions tests, coeliac screen, folate, vitamins A, B12, C, and

D together with early morning cortisol were performed, and the child was started on iron and folate supplements in view of borderline low levels. Dietician and neuropsychology input was sought to improve nutritional intake and to identify possible problematic dietary habits including avoidant/restrictive food intake disorder (ARFID). Over the course of the next few days, his pain was noted to worsen with progressive lower limb proximal muscle weakness. He was also noted to develop a bilateral petechial symmetrical non-tender and palpable rash over both lower limbs together with gum ulcers, gum mucositis and skin bruising. In light of these new symptoms pointing towards possible scurvy, a course of oral high dose vitamin C was initiated. In the interim, vitamin C level results had become available which confirmed very low Vitamin C levels once again. Retrospective review of the MRI images revealed bilateral symmetrical high STIR signal and low T1 signal at the proximal and distal femoral metaphyses. Subtle widening of both distal femoral physis and similar changes throughout the pelvic rim were also seen. These changes were consistent with hypovitaminosis C. Prompt improvement was in fact seen after 3 days of starting treatment, with eventual complete resolution of symptoms over the following weeks.

Tab. 1 Figure showing clinical signs and symptoms of scurvy together with associated imaging, biochemical and haematological findings. Information adapted from Agarwal A. et al. (2015).

System	Clinical Manifestations and Investigation Findings
General	Irritability, Appetite loss, Fever, Iron deficiency anemia, Endocrine disturbance, Cytopenia, Acquired thrombocytopathy, Other vitamin deficiencies
Skin	Petechiae, Rashes, Poor wound healing, Bruising, Hyperkeratosis, Cork screw hairs, Alopecia
Bone (typically symmetrical)	Limp, Arthralgia, Myalgia, Joint swellings, Generalised limb swellings, Scorbutic rosary at costochondral junctions, Sternum depression
	X-ray: Groundglass bone appearance, Osteopenia with cortical thinning, Epiphyseal slipping, Radiodensity metaphyseal physis (line of Franke), Wimburger's sign (radiodense ring around epiphysis), Cupping of distal femoral metaphysis, Subperiosteal haemorrhage in long bones, Pelkan spurs
	MRI: Increased T2 signals in metaphysis of long bones, Widened and striated physis, Haemorrhages at site of fractures
	Ultrasound: bony irregularity, bulky subcutaneous plane, intramedullary/periosteal mass, subperiosteal haemorrhages, multifocal symmetrical signal abnormalities involving metaphyses with associated marrow enhancements
Gums	Swelling, Bleeding, Teeth loosening, Ecchymoses
Mood/psychological	Low moods, Behavioural disturbance

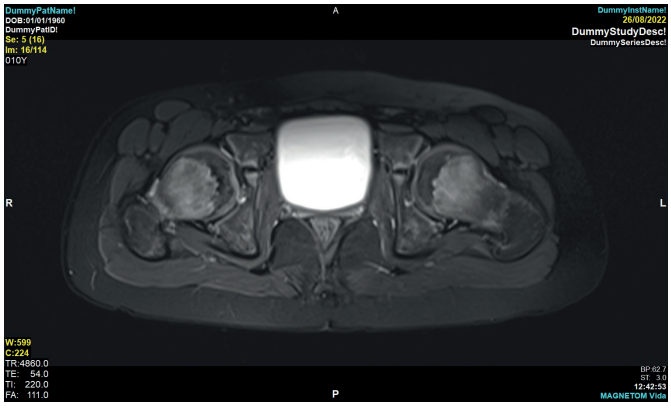

Fig. 1 Axial STIR imaging through both hips and thighs demonstrates the presence of bilateral symmetrical fluid signal characteristics (STIR hyperintense) affecting both the proximal and distal femoral metaphyses.

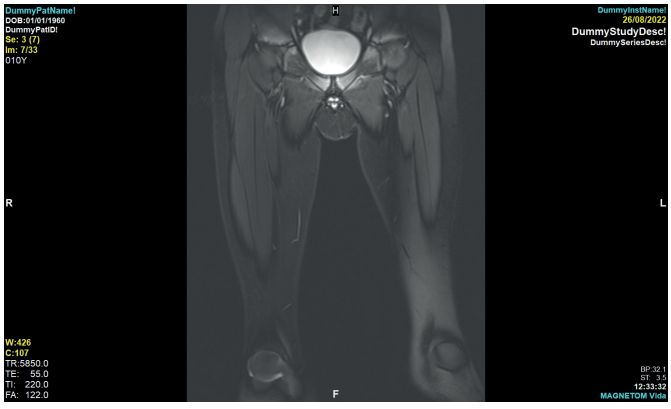

Fig. 2 Coronal STIR imaging through both hips and thighs demonstrates the presence of bilateral symmetrical fluid signal characteristics (STIR hyperintense) affecting both the proximal and distal femoral metaphyses.

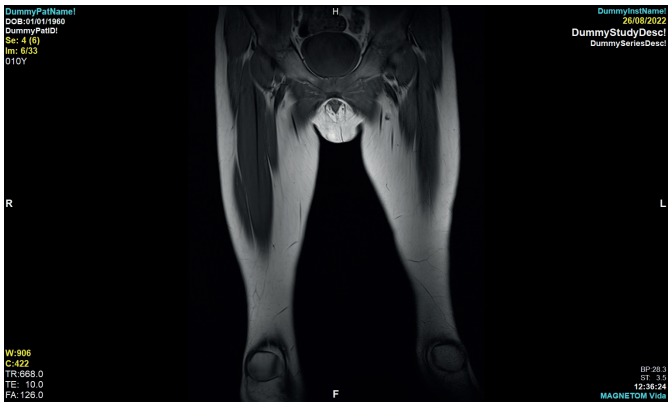

Fig. 3 Coronal T1 weighted view through pubic symphysis showing significant symmetrical marrow oedema like signal changes on either side, along with mild oedema like signal changes extending into the proximal left adductors.

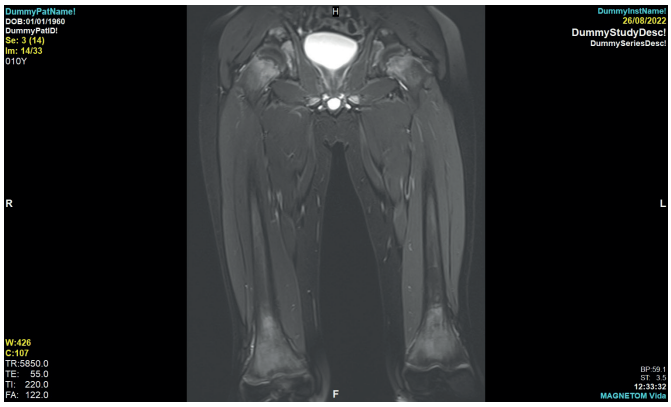

Fig. 4 Subtle, again symmetrical widening of both distal femoral growth plates was also appreciated, as best seen on coronal large FOV STIR imaging.

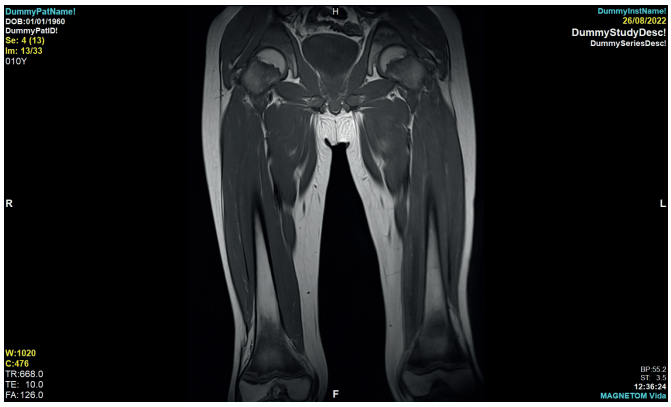

Fig. 5 Coronal T1 weighted imaging through both hips and thighs demonstrates the presence of bilateral symmetrical fluid signal characteristics (hypointense) affecting both the proximal and distal femoral metaphyses. No involvement of the long bone diaphyses or epiphyses was demonstrated.

DISCUSSION

Identification of a high-risk child is of ultimate importance in diagnosing scurvy. At risk groups include not only those with neuropsychiatric or developmental disorders, but also conditions which might affect absorption of water-soluble vitamins (e.g. gastrointestinal conditions), increased vitamin C requirements (e.g children on chemotherapy) or accelerated vitamin C catabolism (e.g conditions with iron overload such as haemochromatosis) (6, 7). Those following special diets including the ketogenic diet are also at risk of developing scurvy and require supplementation and monitoring.

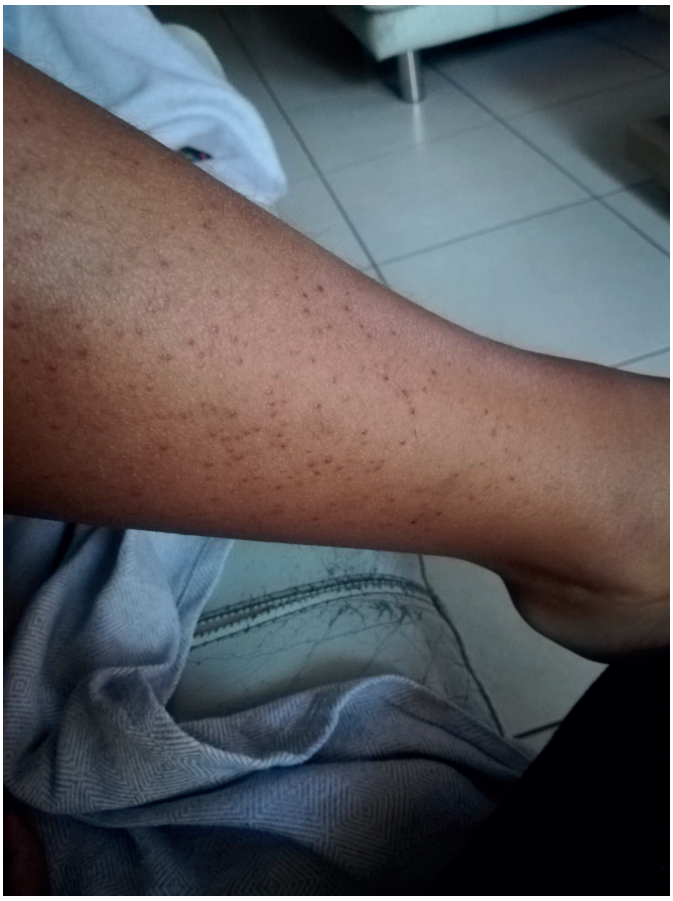

Fig. 6 Image showing the bilateral petechial symmetrical non-tender and palpable rash which had developed over both lower limbs, representative of a diagnosis of hypovitaminosis C.

Despite this, keeping in mind that scurvy can also occur in children without these specific risk factors, a detailed dietary history is important, particularly in unclear cases like the one described above. Fussy eating and selective eating habits are very frequently reported by parents within the paediatric population, especially in early childhood, and these are often disregarded given that this is common behaviour which resolves spontaneously in most. However, disregarded persistent unhealthy eating habits can lead to fundamental nutritional deficiencies and uncertainty regarding whether the abnormal eating behaviour was a cause or a result of an already present deficiency disorder, thus making early detection and treatment important (5). Moreover, given that scurvy is relatively easily treatable with adequate supplementation, timely diagnosis avoids unnecessary, expensive, and painful investigations for the child in question.

The first clinical manifestations of vitamin C deficiency usually appear after one to three months of inadequate intake. Moreover, the earliest signs and symptoms are usually very non-specific such as loss of appetite, low grade fever and malaise, which might not be concerning enough for the parents to seek medical advice. A further

additional diagnostic challenge results from the fact that signs or symptoms may present in an isolated and discontinuous manner, further misleading the clinician and thus contributing to diagnostic delay (8, 9).

Despite classical radiographic signs of scurvy on X-rays being well delineated in the literature, MRI findings are usually non-specific and inconsistent but may be evident earlier than those on X-rays (16–18). Retrospective review of MRI images in our case revealed bilateral symmetrical STIR hyperintensity at the proximal and distal femoral metaphyses, along with subtle widening of both distal femoral physis and similar changes throughout the pelvic bony ring, in keeping with a diagnosis of hypovitaminosis C as per below images.

In our case, the isolated detection of antiganglioside antibodies was misleading for the caring team, leading the team to believe that an immune-mediated nerve disorder was at play and the child was therefore unnecessarily treated with and exposed to IVIG. Monoclonal antiganglioside antibodies against ganglioside monosialic 1 are strongly associated with disorders affecting motor nerves, whilst polyclonal antibodies are found in a subset of patients with Guillain-Barre syndrome and its motor axonal variants. Like other laboratory methods, ganglioside antibody results have variable specificity and sensitivity. Their significance needs to be interpreted in the light of the clinical situation, thus avoiding arriving at a wrong diagnosis of Guillain-Barré Syndrome (GBS) (10, 11).

Measurement of serum vitamin C levels remains the gold standard for the diagnosis of scurvy, defined as levels lower than 2 mg/L. Serum vitamin C levels performed by laboratories are considered to be insensitive (despite being specific) given that they represent serum concentrations which do not always mirror the amount of ascorbic acid stored within body tissues. Moreover, recent vitamin C intake in any form can affect results. Therefore, a diagnosis of scurvy is based on a combination of clinical and radiological findings together with symptoms resolution on initiation of supplementation (12, 13, 21).

Vitamin C supplementation is a relatively cheap and effective medication. There are no standard treatment regimens in place, and individualised doses and treatment duration are advised depending on the severity of the case. Long term vitamin C supplementation is necessary for children who continue to show picky eating behaviour despite multidisciplinary intervention. Vitamin C daily requirements are up to 45 mg per day in children (19). Despite being relatively a safe medication given the body's limited capability to store vitamin C, toxicity from over supplementation has been reported in rare cases. This includes the formation of renal stones and calcium oxalate crystals within the renal tract (19). Commonly reported side effects usually involve gastrointestinal disturbances such as nausea, diarrhoea and abdominal pain, given the osmotic effect of unabsorbed vitamin C (20).

Dietician input in these cases is of utmost importance with reassessment of diet continuing well beyond the acute phase to avoid recurrence of deficiency. Communicating the cause of the child's deficiency and the necessary factors that need modification may be challenging, especially if the other family members have no deficiency and in cases of children with no clear neurodisability and challenging eating behaviour. This therefore necessitates educating and supporting both child and family throughout the entire process of treatment, recovery and follow up. Screening for concomitant vitamin and mineral deficiencies such as B12, folate, calcium, zinc and iron, is also encouraged given vitamin C's role in iron absorption and the high probability of coexistent vitamin deficiencies in children with restrictive food intakes.

CONCLUSION

Despite scurvy being considered to be rare in developed countries, nutritional education and assessment should be given more importance by clinical teams within their practice as part of routine care, with early liaison with dietetics teams for early intervention and early supplementation when indicated. Whilst special consideration should be taken for children within high-risk groups, vitamin C deficiency should be included within the list of differential diagnosis of children presenting with vague constitutional symptoms, haematological, musculoskeletal and mood disorders otherwise unexplained by routine investigations especially for perplexing clinical presentations.

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Oral Candidal Infection Misdiagnosed as a Tumour

Wail Abou Assaf[1], Martin Kapitán[1], Luboš Tuček[1], Jan Laco[2]

ABSTRACT
A case report on a 70-year-old male patient with atypical candidal infection on the palate that was misdiagnosed for a tumour based on clinical examination.
The lesion was an accidental finding when the patient was at a registered dentist for a preventive check-up.

KEYWORDS
oral candidosis; tumour; immunodeficiency; hematological disorders; acquired coagulopathies

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CASE REPORT

The patient comes on the recommendation of a registered dentist for examination of the oral cavity, specifically palate. Patient is treated for type 2 diabetes mellitus, arterial hypertension, with no known allergies. Also, it is mentioned in his history that he had bypass surgery. His medication includes biguanides, dipeptidyl peptidase 4 (DPP-4) inhibitors, direct factor Xa inhibitors, Angiotensin-converting enzyme inhibitors, beta blocking agents, cardiac glycosides, aldosterone antagonists, HMG-CoA reductase inhibitors, peroral glucocorticosteroid. The patient is a non-smoker.

RECENT HEALTH CONDITION

The patient was examined at a registered general dentist, where an accidental finding was seen in the palatal area and an examination at Dentistry Department of the University Hospital Hradec Králové was recommended. The patient reports that the medication was changed from Warfarin (Oral anticoagulant) to Xarelto (direct factor Xa inhibitor) 1 month before. He is not aware of any injury in the area of the lesion, the treatment at the registered dentist took place without anaesthesia. Extraoral and intraoral clinical examination showed face without asymmetry, facial skin without pathological findings, regional lymph nodes not palpable, teeth are incomplete as the patient wears partial removable denture for the upper jaw. Furthermore, blue-violet prominence palpably painless present on the hard palate mucosa without epithelial damage (Figure 1a) could be found. More evident part of the lesion is on the left side of the midline of the size 12 × 15 mm (Figure 1a), other mucous membranes are without pathological findings.

CLINICAL DIAGNOSIS

Traumatic submucosal haemorrhage (due to incorrect brushing technique, suction effect, injury caused by foreign body), capillary haemangioma.

On the first visit at the Dentistry Department of the University Hospital Hradec Králové, it was concluded that it is very likely that the lesion is based on submucosal haemorrhage – very likely that the bleeding is due to medication changes in anticoagulant therapy. As a previous trauma cannot be ruled out, we advised the patient not to traumatize the mucous membrane of the oral cavity (gentle use of toothbrush for instance), and a follow up in one month. After the month during the follow up, the patient did not experience any difficulties and showed no complaints. The extraoral and intraoral clinical examination showed no changes compared with the previous visit. Clinical diagnosis was changed to possibility of tumor, such as haemangioma on the palate and treatment plan was excisional biopsy under sedation.

PROCEDURE

Under analgo-sedation, greater palatine nerve and nasopalatine nerve blocks were done using 4 ml of Supracain 4% (articaine hydrochloride 40 mg and 1 : 200,000 0.005 mg/ml adrenaline – Zentiva, ČR) local anaesthetic was injected, in attempt for anaesthesia and bleeding control. Excisional biopsy was made with the use of scalpel Blade 15, in addition for electrocoagulation device for haemostasis. Specimen excised was of 2 cm × 2 cm including the safe margins of 0.5 cm. The defect on the palate was covered with Surgicel (Oxidised regenerated cellulose, absorbable haemostat – Ethicon New Jersey, USA) stitched to the margins of the palatal mucosa, as shown in (Figures 1a and 1b). The specimen was sent to histopathological examination. The patient came a week later for a check-up and showed no complaints. Histological findings: In the surface squamous epithelium, especially in the superficial parts, there are numerous neutrophilic granulocytes and fungal fibres with the appearance of candida (positive silver staining according to Grocott). Beneath epithelium, there is mixed inflammatory infiltrate with foci of old and recent haemorrhage and scaring. Due to the fragmentation of the material, it is difficult from a microscopic point of view to reliably comment on the completeness of the lesion removal. Dysplastic changes or malignant tumor were not present. Swab for cultivation was made for further treatment at the periodontology and oral diseases department, and as initial treatment Borax glycerine and chlorohexidine mouth washes were prescribed.

On the third follow up, the patient stated that for 14 days he experienced flu symptoms, (cough, runny nose) – the patient was complaining of fluid coming out of his nose while drinkng or rinsing. Based on clinical examination, 2 mucosal defects were present on the hard palate, one was on the left side with exposed necrotic bone. The

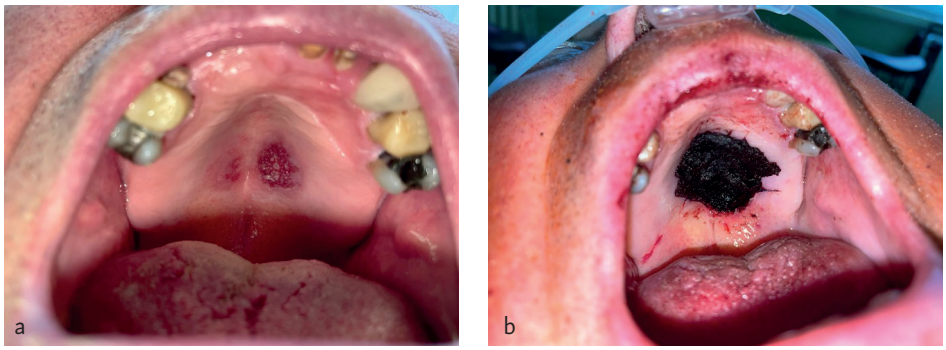

Fig. 1 (a) Picture of the patient's oral cavity, focused on the lesion located on the palate. (b) Picture showing absorbable haemostat (Ethicon, New Jersey, USA) stitched to the margins of the palatal mucosa after the excision of the lesion.

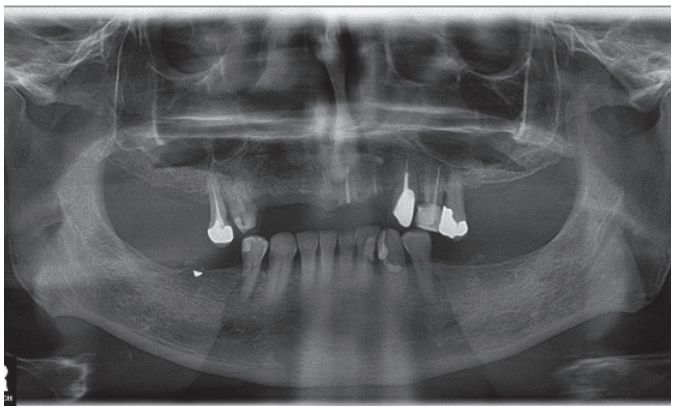

Fig. 2 OPG: Incomplete dentition, radixes 21, 22, teeth 15, 24, 23 endodontically treated in the area of 46 six we can see small radiopaque particle with estimated size 2 × 1 mm – probably part ost the amalgam filling, which was not remove during extraction of 46.

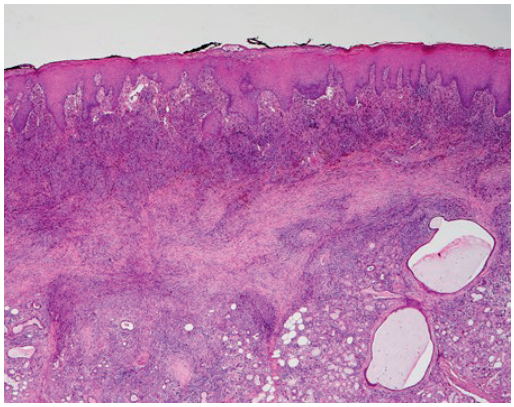

Fig. 3 On the surface of the specimen there is acanthotic squamous epithelium. Beneath epithelium there is mixed inflammatory infiltrate with haemorrhage and scaring extending to the minor salivary gland with dilated ducts (bottom right). (Hematoxylin-eosin, original magnification 40×)

Note: The black dye on the epithelial surface is the artificially flowing ink used during handling of the specimen to mark the resection margins.

other defect was in the midline of the hard palate, with oronasal fistula that was possible to probe. As a temporary treatment, the defects were etched with 30% hydrogen-peroxide and an operation was planned for closing the oro-nasal communication, otherwise there were no signs of recurrence of the lesion.

DISCUSSION

Benign red lesions in the oral cavity can be associated with systemic diseases, especially haematological disorders. Megaloblastic anaemia also known as pernicious anaemia is associated with Moeller-Hunter glossitis (Beefy-Red tongue). Morbus Rendu-Osler-Weber also known as telangiectasia hereditaria hemorrhagica, shows multiple telangiectasis and small angiomas in the oral cavity. Acquired coagulopathies also play a role in formation of red lesions, such as patients using oral anticoagulants as small ecchymosis or hematomas can be noticed on different body parts including the oral cavity if a small injury was experienced.

To a more serious extent, malignant lesion can also be included in the differential diagnosis, persisting red lesions in the oral cavity can encompass extra-nodal lymphomas, leukemias (more specifically acute myeloid leukemias), carcinom in situ in cases of erythroplakia or atypical presentation of squamous cell carcinoma in which complaints such as pain will evoke in progression of the lesion and ulceration.

These lesions often manifest in different shades of redness, which makes their identification crucial in oral examinations. Extra-nodal lymphomas and hematological malignancies can present as a painless palpable mass in the oral cavity, while squamous cell carcinoma, the most common oral cancer can exhibit a reddish non ulcerative appearance unlike the usual.

Red malignant lesions can also be encountered in suppressed immunity, Kaposi's sarcomas caused by Human herpesvirus 8 can be seen in patients with altered immunity, such as HIV positive patients or patients on immunosuppressants medications after organ transplants.

Speaking of immunity, autoimmune diseases such as pemphigoid, pemphigus in addition to linear IgA disease take a spot in the list of red lesions in the oral cavity. Identification of these disorders is essential for therapy planning, ranging for surgical excision and chemotherapies/radiotherapies for malignant lesions to immunosuppressive medications in autoimmune diseases.

Mycotic infection in the oral cavity represents in most cases oral candidosis. The major causes of candidosis are due to Candida albicans or non-albicans species such as (C. glabrata, C. crusei, C. tropicalis a C. dubliniensis). Predisposing factors can be local and systemic. Systemic factors include endocrine and metabolic disorders (eg. diabetes mellitus), haematological disorders -Marrow aplasia, and primary/secondary immunodeficiency. Regarding local factors, bad oral hygiene comes in the first place as plaque accumulation gives a substance for overgrowth. Hyposilia, prosthesis and the use of corticosteroids also play a role, too. Candidal infections, especially chronic erythematous form that is associated with complete or partial prosthesis are treated with anti-mycotics and good oral hygiene. Anti-mycotics involve several groups {Imidazole, Triazoles, Polyens, Allylamines}. Some of these medications should be avoided in the case the patient is on certain drugs as there can be drug-interactions.

Drugs such as Ketoconazole-from the Imidazole group and Itraconazole-from the Triazol group, can interact with medications such as steroids, CyA, carbamazepine, digoxin and oral anticoagulant (Warfarin).

In addition to that these drugs should not be given with medication that affect the stomach acidity, such as parasympatholytic and H2 blockers as it leads to poor absorption of the anti-mycotic in the absence of adequate acidity.

Oral candidoses that are associated with red lesions can be acute erythematous candidosis, were the patient complains of tactile tenderness and pain on palpation of the affected area. Usually, this type of candidal infections is seen in patients with good health but in their history, they have been treated with broad spectrum antibiotics causing the bacterial flora to decrease allowing the flourishing of fungal organisms.

The other type is chronic erythematous, also known atrophic prosthetic candidosis, with chief complaints of burning sensation and pain. The lesion is present at the site of prosthesis (eg. Complete denture). These common symptoms were not present.

PATIENTS CONSENT

The consent to publish this information was obtained from study participant. We confirm that written proof of consent to publish study participants are available when requested and at any time.

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