ISSN 2149-7893 • EISSN 2536-507X

Indexed in Web of Science

Official journal of
Cyprus Turkish Medical Association

CYPRUS JOURNAL OF MEDICAL SCIENCES

VOLUME 2 • ISSUE 3 • DECEMBER 2017

AVES

www.cyprusjmedsci.com

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Publication Type
Local periodical

Printed Date
August 2017

Printed at
Share Ajans, Şehit Fevait Ali Sok. Dük. No: 4 C, Sönmezler Apt, Göçmenköy, Nicosia, Cyprus

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Original Article

DOI: 10.5152/cjms.2017.273

Impact of Breast Tomosynthesis for Evaluating Specimen of Breast Carcinoma: Initial Results

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Cite this article as: Başara Akın I, Balcı P, Gezer NS, Durak MG, Tunal KÇ, Aksoy SÖ. Impact of Breast Tomosynthesis for Evaluating Specimen of Breast Carcinoma: Initial Results. Cyprus J Med Sci 2017; 2: 47-51.

BACKGROUND/AIMS
To evaluate the impact of digital breast tomosynthesis (DBT) for assessing specimens of breast carcinoma (BCa) in terms of comparing with other diagnostic tools.

MATERIALS and METHODS
Between November 2014 and May 2015, patients who underwent wire-guided breast biopsy with mammography (MG), specimen radiography (RG), and digital specimen tomosynthesis (DST) examinations were evaluated. Two breast radiologists retrospectively assessed the results in consensus. Breast lesions were classified according to the Breast Imaging Reporting and Data Systems (BI-RADS). In mass described cases, the longest axes of the masses were measured; and in calcification described cases, the longest axes of the calcifications were measured. All findings were compared with macroscopic measurements. Statistical analyses were performed; $p<0.05$ was considered significant.

RESULTS
In total, 85 specimens were evaluated. The mean age was 54.2±10.8 years. Of the 85 specimens, 46 lesions were malignant and 39 lesions were benign. The average mass sizes were 14±9.7 and 13±6.8 mm in diagnostic MG and DBT, respectively. In specimen RG and DST, the average mass sizes were 12±6 mm and 12±6.2 mm, respectively. The mean macroscopic mass size was 12±6.3 mm. There was a statistical significant difference between diagnostic MG and specimen RG-DST findings regarding mass sizes ($p=0.02$ and $p=0.01$, respectively). BI-RADS evaluations of specimen RG and diagnostic and specimen TS were similar but different from those of diagnostic MG ($p<0.001$).

CONCLUSION
The exact detection of BCa specimen and its BI-RADS features can be diagnosed using DST; lesion size, with specimen and diagnostic DBT. Additionally, DBT can help diagnose preoperative structural distortion or asymmetric densities.

Keywords: Breast carcinoma, digital breast tomosynthesis, digital specimen tomosynthesis

INTRODUCTION

Breast carcinoma (BCa) is the most common cancer and the second leading cause of death in women worldwide (1). Early detection of BCa can help decrease mortality and morbidity (2). Mammography (MG) is a prevailing imaging method for determining early BCa (3-5). However, the superimposition of dense breast tissue on MG is a significant handicap for diagnosis (6, 7). To solve this obstacle, additional diagnostic methods such as MG follow-up, ultrasonography, and magnetic resonance imaging are used (8). All these are mostly used for benign lesions and can cause anxiety with high health care costs. In recent years, digital breast tomosynthesis (DBT) is an emerging diagnostic tool to be used to overcome overlapping the breast tissue (8). The DBT system acquires multiple projection images by a rotating X-ray tube around a digital detector. Three-dimensional (3D) images are derived from the reconstruction of two-dimensional (2D) data (8).

Of 25%-35% of early BCas, the tumor is nonpalpable at the time of diagnosis (9). These lesions are defined as asymmetric densities, deep seated lesions, and calcifications (10). Current published literature suggests breast-conserving therapy, including lumpectomy or wide-to-local excision together with adjuvant radiotherapy to the tumor bed in patients with nonpalpable lesions

This study was presented at the 37th National Radiology Congress, 01-06 November, Antalya, Turkey.
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Received: 18.08.2017
Accepted: 15.10.2017
Available Online Date: 09.01.2018

(11). Breast-conserving surgery is considered the reference standard treatment for early BCa (12). Irradical resection of nonpalpable lesions varies between 13% and 58% (10). The most commonly used, oldest, and reference standard method for resection with minimal but sufficient margin is wire-guided needle biopsy (13). Specimen radiography should be performed and the findings of specimen radiography should be evaluated with preoperative MG. This evaluation provides us to confirm the exact localization of excised lesion and to determine whether complete resection is realized during operation.

Tumor size is commonly measured on MG and/or ultrasonography. However, these techniques are valuable in patients who have dense breast tissue and underestimate tumor size. Breast structures are superimposed on to 2D plane; therefore, tumor outlines might be obscured in MG examination (14). Some of the studies recently published pointed out that the application of DBT might improve lesion margin visibility; as a result, it is an effective method for lesion characterization and diagnosis of early BCa (15-17). Despite all these proven data, there is a lack of study including DBT features on removed breast tissue during the operation in terms of comparing with other diagnostic tools in the published literature.

We aimed to evaluate the characterization of tumors using the Breast Imaging and Reporting Data System (BI-RADS) classification and to compare the tumor sizes in preoperative diagnostic MG and DBT, perioperative specimen radiography, digital specimen tomosynthesis (DST), and pathologic findings using breast specimens. To the best of our knowledge, this is the first study to compare specimens from the published literature.

MATERIALS and METHODS

This study included a retrospective view of prospective recorded data. Radiology and pathology database of Dokuz Eylül University School of Medicine were investigated. All data were recorded. The study was approved by the Institutional Review Board of our institute. The protocol number of noninterventional investigation ethical committee approval was 2828 and decision number was 2016/21-02. Signed consent forms were obtained from all patients. Exclusion criteria were ultrasonography-guided wire biopsy patients and irregular and missing data.

Data Collection

Between November 2014 and May 2015, patients who underwent breast wire-guided biopsy with MG and specimen radiography tomosynthesis examinations were evaluated. The review was retrospectively performed by two breast radiologists (one senior and one junior) in consensus. Data collection was performed using Picture Archiving and Communication System (ISite Radiology 4.1.11.0.0, Philips, Koninklijke, The Netherlands). MG and specimen radiography tomosynthesis were performed using digital MG and DBT device (Selenia® Dimensions®, Hologic, Marlborough, MA, USA). Each case had four images in standard modalities (i.e., one craniocaudal and one mediolateral oblique view of the left and right breast), with additional positions if needed, preoperative wire-marked breast image with wire, postoperative specimen radiography and tomosynthesis. In mass described cases, the longest axis of the masses was measured; and in calcification described cases, the longest axis of the calcifications was measured. The findings were compared with macroscopic measurements. Breast lesions were characterized according to the BI-RADS classification. The imaging findings before and after wire-guided biopsy are shown in Figure 1-3.

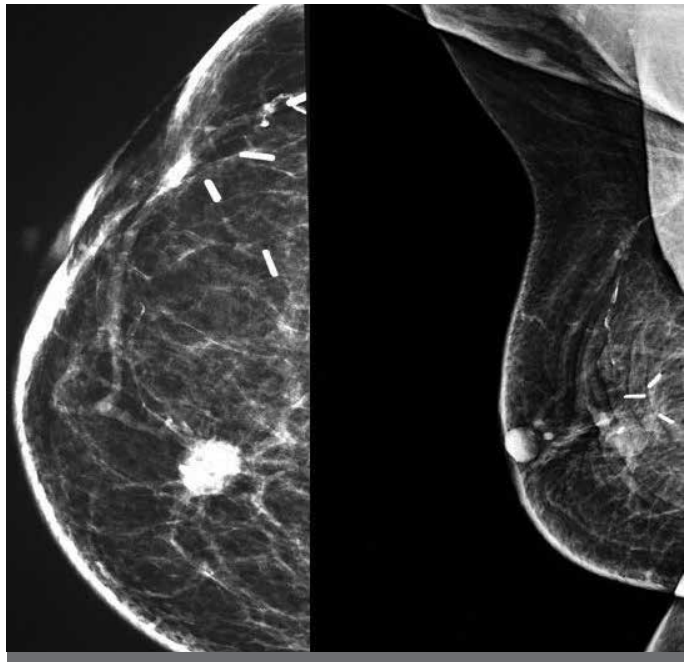

FIGURE 1. In a 79-year-old female patient, a round-shaped, spiculated margined BI-RADS 5 lesion is observed in her right breast, at inner quadrant, 3 o'clock localization

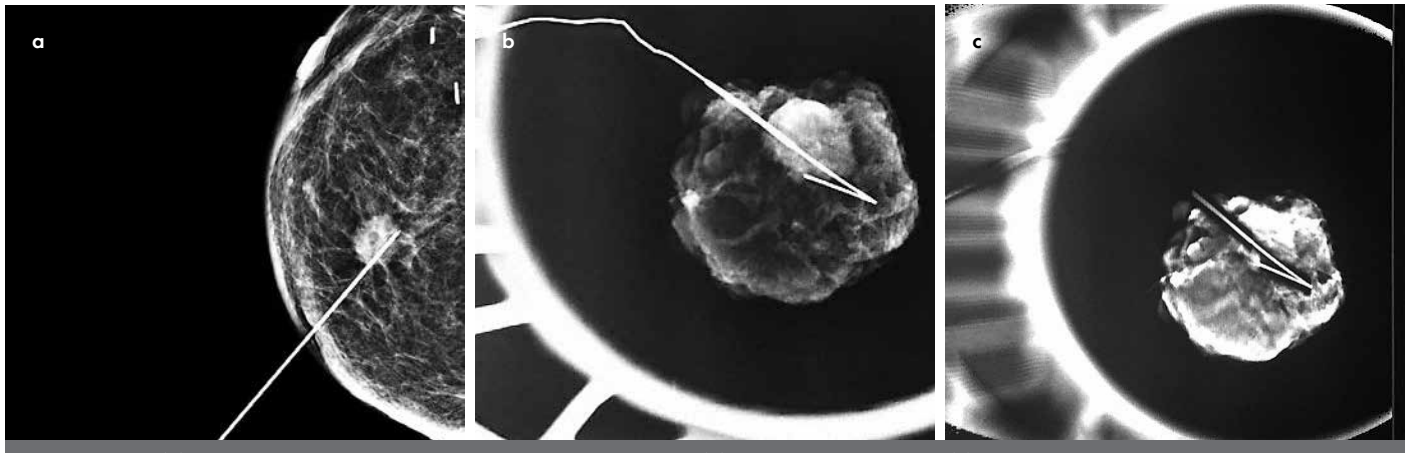

FIGURE 2. a-c. (a) Wire-guided biopsy with mammography is performed, (b) specimen radiography, (c) tomosynthesis images

Breast Imaging Reporting and Data System

All patients were reviewed according to the recent BI-RADS (5th edition, 2013) lexicon of MG and examination. All patients underwent preoperative MG and DBT, and the specimens were preoperatively evaluated with radiography and tomosynthesis.

Statistical Analyses

All statistical analyses were performed using Statistical Package for Social Sciences version 22.0 (IBM Corp.; Armonk, NY, USA) software. The sizes, measured in all examinations and pathologic evaluations, were compared with one-way analysis of variance test. Independent variables were compared with paired t test, and $p<0.05$ was accepted as statistically significant.

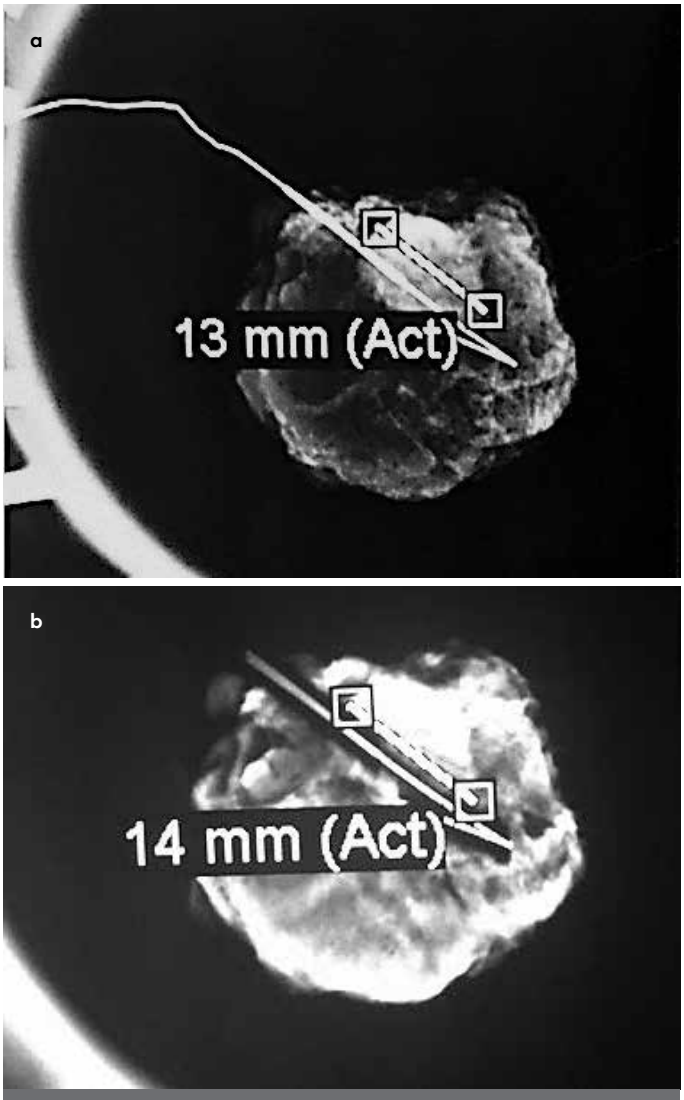

Figure 3. a, b. (a) The size of the mass in specimen radiography was 13 mm, (b) the size of the mass in tomosynthesis was 14 mm (*Histopathology: Invasive ductal carcinoma*)

RESULTS

Results of Demographic Data

The total number of patients was 85, and the mean age was 54.2±10.8 years. Forty-six (54%) lesions were malignant, and 39 (45%) lesions were benign. According to the longest axis evaluation, the average mass sizes were 14±9.7 and 13±6.8 mm in diagnostic MG and DBT, respectively. In specimen radiography and specimen tomosynthesis, the average mass sizes were 12±6 and 12±6.2 mm, respectively. The macroscopic average mass size was 12±6.3 mm. When average sizes were compared, there was no statistical significance between specimen radiography and tomosynthesis findings. All these results are summarized in the cross-correlation table (Table 1).

Breast Imaging Reporting and Data System

Breast Imaging and Reporting Data System classifications intended for the lesions and calcifications were separately performed for all three imaging tools. In MG examinations, one patient was evaluated as BI-RADS 3 and 78 were evaluated as BI-RADS 4 (39- BI-RADS 4A, 27- BI-RADS 4B, and 12- BI-RADS 4c). Six patients were diagnosed as BI-RADS 5. In DBT, one patient was detected as BI-RADS 3 and 74 were diagnosed as BI-RADS 4 (36- BI-RADS 4A, 19- BI-RADS 4B, and 19- BI-RADS 4C). Ten patients were evaluated as BI-RADS 5. Specimen radiography examination revealed that two patients were BI-RADS 3 and 80 were BI-RADS 4 (51- BI-RADS 4A, 23- BI-RADS 4B, and 6- BI-RADS 4C). In DST, two patients were evaluated as BI-RADS 3 and 78 were evaluated as BI-RADS 4 (39- BI-RADS 4A, 27- BI-RADS 4B, and 12- BI-RADS 4C). Six patients were diagnosed as BI-RADS 5.

Breast Imaging and Reporting Data System evaluations of specimen radiography, specimen tomosynthesis, and DBT were similar. However, these findings were different from those of diagnostic MG. When BI-RADS 3 lesions were accepted as benign, BI-RADS 4 and 5 lesions were accepted as malignant between DBT and specimen tomosynthesis; and there was statistical significance for diagnostic MG findings ($p<0.001$) (Table 2).

Comparison of Diagnostic Tools

When the pathologic sizes of the lesions were considered, we found a statistical significance between diagnostic MG, specimen radiography, and specimen tomosynthesis findings

TABLE 1. Comparison of mammography, tomosynthesis, specimen radiography, and pathology sizes in cross-correlation table

Parameter	Mean size in MG 14±9.7	Mean size in DBT 13±6.8	Mean size in specimen RG 12.2±6	Mean size in DST 12±6.2	Mean size in pathology 12.4±6.2
Mean size in MG 14±9.7	-	p=0.2	p=0.02*	p=0.01*	p=0.08
Mean size in DBT 13±6.8			p=0.1	p=0.06	p=0.2
Mean size in specimen RG 12.2±6				p=0.1	p=0.7
Mean size in DST 12±6.2					p=0.5

MG: mammography; DBT: digital breast tomosynthesis; RG: radiography; DST: digital specimen tomosynthesis
Paired t test was used.
*Statistical significant p value

TABLE 2. Breast Imaging and Reporting Data System (BI-RADS) comparison according to different methods in the same patient group

Parameters	BI-RADS score	N	p
MG	3	1	<0.001*
	4A	39	
	4B	27	
	4C	12	
	5	6	
DBT	3	1	
	4A	36	
	4B	19	
	4C	19	
	5	10	
Specimen RG	3	2	
	4A	51	
	4B	23	
	4C	6	
	5	3	
DST	3	2	
	4A	39	
	4B	27	
	4C	12	
	5	6	

MG: mammography; DBT: digital breast tomosynthesis; RG: radiography; DST: digital specimen tomosynthesis
*Statistical significant p value

(p=0.02 and p=0.01). However, there was no statistical significant difference among DBT, specimen radiography, specimen tomosynthesis, and the results with pathologic average sizes. All these results are summarized in the cross-correlation table (Table 1).

DISCUSSION

Digital breast tomosynthesis is a diagnostic modality for BCa and its screening (8, 18). It is a 3D imaging technique obtained by reconstruction of 2D images during standard mammographic compression. Thus, the interference of breast tissue overlapping can be reduced by this way. Additionally, as it provides conspicuity of invasive cancers, false-positive results can be reduced (8, 18). The present study aimed to characterize the tumors using BI-RADS classification and to compare the tumor sizes in preoperative MG and DBT, perioperative specimen radiography, specimen tomosynthesis, and pathologic findings using breast specimens. When BI-RADS 3 lesions were accepted as benign, BI-RADS 4 and 5 lesions were accepted as malignant; there was statistical significance between DBT specimen tomosynthesis and diagnostic MG findings. The BI-RADS evaluations of specimen radiography, specimen tomosynthesis, and DBT were similar. When the pathologic sizes of the lesions were considered, there were statistical significances among diagnostic MG, specimen radiography, and specimen tomosynthesis findings; there was no statistical significance between specimen radiography and specimen tomosynthesis findings.

In our study, the average mass sizes of the lesions were 14±9.7 and 13±6.8 mm in diagnostic MG and DBT, respectively. In specimen radiography and specimen tomosynthesis, the average mass sizes were 12±6 and 12±6.2 mm, respectively. The macroscopic average mass size was 12±6.3 mm. The study published by Fornik et al. (19) concluded that DBT was superior to MG for evaluating both lesion measurement and stage. In the present study, we focused on comparing specimens. DBT, specimen radiography, specimen tomosynthesis, and the results with pathologic average sizes had no statistical significance. The average lesion sizes measured from specimen tomosynthesis were similar with avarage macroscopic sizes. Considering this, our findings were compatible with the literature (19).

The BI-RADS evaluations of specimen radiography, specimen tomosynthesis, and DBT were similar. However, these findings were different from those of diagnostic MG in our study. BI-RADS 3 lesions were accepted as benign. Conversely, BI-RADS 4 and 5 lesions were accepted as malignant. Thus, specimen tomosynthesis DBT and diagnostic MG findings had statistically significant differences. Raghu et al. (20) concluded that working up with DBT significantly improves diagnostic accuracy and confidence. Adding DBT to digital MG for screening can provide many benefits including greater sensitivity in dense breast tissue. After using DBT, the accuracy of MG and true BI-RADS characterizations of lesion pointed the visual separation of the overlapping tissues (21). Our results were compatible with their findings. Nevertheless, our findings and similar previous studies mentioned above should be checked again with high number of participants for providing more benefits on clinical usage of tomosynthesis.

The preoperative measurement of the exact lesion size in patients with BCa is very important in terms of clinical staging and decision of correct surgical treatment, specifically breast-conserving therapy (19). This is also one of the significant prognostic factors of BCa (22-24). Evaluation of specimens in perioperative process, detection of lesion extension, and measurement of lesion size are corner stones for making the decision in operative adequacy. In the current study, there was no statistical significance between specimen radiography and specimen tomosynthesis. All the measured sizes from the specimens were similar to the histopathologic results. Nevertheless, there is a very small difference, and specimen tomosynthesis findings were more similar than specimen radiography findings. This finding reveals that specimen tomosynthesis is more reliable in the decision of total lesion excision. Thus, preoperative specimen tomosynthesis may show a surgical way to determine the margins of cancer tissue.

There are some limitations to this study. The first one is small number of patients. However, our clinic is a reference clinic with high patient volume; we have performed many image-guided needle biopsy studies. Besides, the number of patients with all complete images was limited. Additionally, we performed specimen radiography for all needle-guided biopsy, and we excluded the patients who underwent ultrasonography-guided needle biopsy. Because of difficult measuring of specimen radiography, we also excluded some of the patients with microcalcifications in breast. Nonetheless, we focused on the importance of specimen tomosynthesis in patients with BCa. Although we noted some different statistically significant differences in this study, more studies are needed to evaluate clinical benefits.

Our study is the first and unique study that evaluated and compared the specimens in terms of lesion sizes and BI-RADS characterization in the published literature. Accurate evaluation of specimen will assure the surgeon for the adequacy of the surgery. Additionally, during the operation, this can provide them to make correct decisions for surgical techniques. As specimen tomosynthesis enables visual separation of the overlapping tissues, more accurate evaluation can be performed.

For surgical treatment, it is very important to determine the exact surgical margins of BCa. DBT can easily diagnose BCa and determine the precise location of lesion. More studies with high number of patients are needed for accurate diagnosis and determination of BCa lesion margins.

Ethics Committee Approval: Ethics committee approval was received for this study from the Institutional Review Board of Dokuz Eylül University School of Medicine (Decision No: 2016/21-02).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - I.B.A., P.B.; Design - P.B.; Supervision - I.B.A.; Resource - M.G.D., S.Ö.A.; Materials - S.Ö.A.; Data Collection and/or Processing - I.B.A., P.B., M.G.D.; Analysis and/or Interpretation - I.B.A., P.B., M.G.D.; Literature Search - K.Ç.T., N.S.G.; Writing - I.B.A.; Critical Reviews - P.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Original Article

DOI: 10.5152/cjms.2017.304

Advanced Stage Buccal Carcinoma: Effect of Local Extension on Prognosis

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Cite this article as: Cömert E, Tunçel Ü, Turan F, Kılıç C, Atabey P. Advanced Stage Buccal Carcinoma: Effect of Local Extension on Prognosis. Cyprus J Med Sci 2017; 2: 52-6.

BACKGROUND/AIMS
The aim of this study was to evaluate the effects of alveolar mucosa, bone, cheek skin, and lip invasion of buccal carcinoma on locoregional recurrence and survival rates.

MATERIALS and METHODS
The study included 36 patients with T3-T4a buccal carcinoma. Both T3 and T4a tumors were divided into two subgroups: T3 tumors limited to buccal mucosa, T3 tumors with the involvement of alveolar mucosa, T4a tumors with bone invasion, and T4a tumors with skin and/or lip invasion.

RESULTS
In T3-T4a tumors, the rates of tumors limited to the buccal mucosa, tumors involving alveolar mucosa, bone of either the maxilla or mandible, and skin and/or lips were 25%, 22.2%, 33.3%, and 19.4%, respectively. The 3-year disease-free survival rate of patients with T3 and T4a tumors was 70.6% and 52.6%, respectively. The 5-year disease-free survival rate of patients with T3 and T4a tumors was 58.8% and 42.1%, respectively. Regarding the 3- and 5-year survival rates, no statistically significant difference was observed between T3 and T4a tumors and between their subgroups.

CONCLUSION
Despite the lack of statistical significance, there seemed to be a trend toward worse survival among the patients with bone invasion.

Keywords: Buccal mucosa, cancer, survival

INTRODUCTION

Carcinoma of the buccal mucosa is a rare and aggressive tumor of the oral cavity. The buccal area is defined as the mucosal lining of the cheeks and lips from the oral commissure anterior to the pterygomandibular raphe and posteriorly merging with the alveolar ridges superiorly and inferiorly. The anatomic barriers within the buccal space provide almost no resistance to tumor spread, and this feature of the buccal space was shown as the major reason why buccal carcinoma acts more aggressively than those originating in other subsites in the oral cavity (1-3).

Treatment for stage I and II buccal carcinoma has been either surgery or radiation therapy as a single modality. For advanced stage tumors, surgical excision combined with postoperative radiotherapy is the main treatment modality. Therapeutic neck dissection has been performed in early stage tumors with neck metastasis and in all advanced stage tumors. (2, 4, 5).

This study was presented at the 35th National Otolarngology and Head and Neck Surgery Congress, November 2013, Antalya, Turkey.

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Received: 16.11.2017 **Available Online Date:** 09.01.2018
Accepted: 27.11.2017

The involvement of the maxilla, mandible, cheek skin, and lips lead to varied and morbid resections and may affect the prognosis of the tumor. The aim of this study was to evaluate the effects of alveolar mucosa, bone, cheek skin, and/or lip invasion of buccal carcinoma on locoregional recurrence and survival rates.

MATERIALS and METHODS

Records of patients from 2003 to 2012 were reviewed. Thirty-six patients were categorized as having T3-T4a buccal squamous cell carcinoma. Tumors with significant extension to other portions of the oral cavity or oropharynx making the primary site unclear and tumors that were not primarily treated by surgery were excluded. The medical charts were retrospectively reviewed to determine patient's age, sex, tumor site, pathologic staging, differentiation, margin status, involvement of other subsites of the oral cavity, treatment, recurrence, and survival.

All the patients were treated through en-block resection of the primary site and unilateral selective (level I-2-3), modified radical, or radical neck dissection. If the tumor was extended to the mucosa of the alveolar process and hard palate or had invaded the mandible and/or maxilla, marginal or segmental mandibulectomy and/or partial or hemimaxillectomy was performed for adequate margins. The defects were reconstructed either with full thickness skin graft or with local flaps. Selective (level I-2-3) neck dissection was performed for a clinically N0 neck, and modified radical or radical neck dissection was performed when clinically positive neck lymph nodes were detected. Tumors were staged retrospectively according to the tumor, node, metastasis (TNM) staging system, as proposed by the seventh edition of American Joint Committee on Cancer (AJCC) (6). Tumors extending to the mucosal side of the alveolar process and hard palate without bone invasion were considered T3 tumors. Tumors involving lips, skin, and bony structures of the maxilla and mandible were considered T4a tumors. All the T3 tumors were sized >4 cm, but a group of them extended to the mucosa of the alveolar process of either maxilla or mandible. Thus, T3 tumors were divided into two groups: T3 tumors limited to the buccal area and T3 tumors involving the alveolar mucosa. All the T4a tumors included in the study had either invasion of the alveolar process of the maxilla/mandible or skin/lips and hence they were also divided into two groups: T4a tumors with bone (maxilla or mandible) invasion and T4a tumors with lips and/or skin invasion.

Postoperative radiotherapy was performed on patients with pathologic T4a tumors, positive surgical margins, multiple lymph node metastasis, and extracapsular spread. Irradiation was started within 4-6 weeks post operation. Radiation dosage ranged as 60-66 Gy. The prescribed dose was 1.8-2.0 Gy per fraction per day administered 5 days a week for 6 weeks.

The study was approved by the local institutional review board. As the study was based on the retrospective analysis of the survival, patients' consent was not required.

TABLE I. Clinical and surgical parameters of 36 patients with buccal carcinoma

Variable		n	%
Sex	Male	22	61.1
	Female	14	38.9
Location	Only buccal mucosa	9	25
	Alveolar mucosa involvement	8	22.2
	Bone invasion	12	33.3
	Lips and skin invasion	7	19.4
Tumor thickness	Mean	10.4	
	≤4 mm	7	16.6
	>4 mm	29	83.3
Histological differentiation	Well	19	52.7
	Moderate	9	25
	Poor	8	22.2
T stage	T3	17	47.2
	T4a	19	52.8
N stage	N0	18	50
	N1	8	22.2
	N2	10	27.7
Excision margins (mm)	Positive	9	25
	≤5 mm	7	16.6
	>5 mm	20	55.5

T: tumor stage; n: number of patients; p: statistical analysis of recurrence rates between T3 and T4a tumors with log-rank test

TABLE 2. Summary of pathological findings by stage

T	Well differentiated	Moderately differentiated	Poorly differentiated	Positive margins
T3 buccal mucosa I	4	2	3	
T3 alveolar mucosa involvement	3	4	1	1
T4a bone invasion	7	3	2	5
T4a lip or skin invasion	5	-	2	2
Total	19	9	8	9

T: tumor stage; p: statistical analysis of disease-free survival between subgroups with log-rank test

Univariate association with disease-free survival was evaluated using the Kaplan-Meier analysis and tested using the log-rank test. Two-tailed p values of ≤0.05 were considered statistically significant. The Statistical Package for Social Sciences, version 16.0 (SPSS Inc.; Chicago, IL, USA) program was used for statistical analysis.

RESULTS

The group studied consisted of 36 patients (T3-T4a buccal carcinoma) with a mean age of 57 years (28-75 years). The

clinical and histological parameters are summarized in Table I. Of these 36 patients, 17 (47.2%) had T3 disease and 19 (52.8%) had T4a disease. The histopathology of tumor differentiation showed that most patients (52.8%) had well-differentiated tumors. The summary of the pathologic findings by stage is provided in Table 2. The distribution of tumors according to its extension to the adjacent sides of the oral cavity and skin and their N status are presented in Table 3.

Among all the tumors included to the study, the rate of T3 tumors limited to the buccal mucosa was 25% (n=9); the rates of involvement of the alveolar mucosa, bone of maxilla or mandible, and skin and/or lips were 22.2% (n=8), 33.3% (n=12), and 19.4% (n=7), respectively. A pathologic examination of the neck dissection specimens of these groups of patients revealed metastatic lymph nodes in 44.4% (n=4), 62.5% (n=5), 50% (n=6), and 42.8% (n=3) patients, respectively. In our series, 24 patients (66.7%) required adjuvant radiotherapy in addition to surgical management.

Excision of the bony structures of the hard palate and alveolar process of the mandible and maxilla was performed in 55.5% (n=20) of our patients. In the pathological examination, invasion of the bone was observed in 60% (n=12) of the patients.

The mean follow-up time for all patients was 84 months (range, 62-152). The mean time between initial treatment and locoregional recurrence for the entire group was 21.7 months (range, 9-27 months). Locoregional recurrence developed in 18 (50%) patients during follow-up. Among them, 9 (50%) had disease recurrences only at the primary sites, 4 (22.2%) had recurrences only in the ipsilateral neck, and 5 (27.7%) had simultaneous primary and neck recurrences. Five of these patients underwent salvage surgery followed by palliative radiotherapy, and the remaining received only palliative radiotherapy.

The 3- and 5-year recurrence rates of T3 tumors were 29.4% and 41.2%, respectively. The 3- and 5-year recurrence rates of T4a tumors were 47.4% and 57.9%, respectively. With regard to 3- and 5-year recurrence rates, no statistically significant difference was observed between T3 and T4a tumors based on the log-rank test (p>0.05). The data are presented in Table 4.

The 3-year disease-free survival rate of patients with T3 and T4a tumors was 70.6% and 52.6%, respectively. The difference was not statistically significant (p=0.282 using log-rank test). The 5-year disease-free survival rate of patients with T3 and T4a tumors was 58.8% and 42.1%, respectively. The difference was not statistically significant (p=0.324).

The 3-year disease-free survival rate of patients with T3 tumors limited to the buccal mucosa and T3 tumors involving the alveolar mucosa was 66.7% and 75.0%, respectively. The 5-year disease-free survival rate of patients with T3 tumors limited to the buccal mucosa and T3 tumors involving the alveolar mucosa was 66.7% and 50%, respectively. The 3-year disease-free survival rate of patients with T4a tumors with bone invasion and T4a tumors involving skin and/or lip was 50% and 57.1%, respectively. The 5-year disease-free survival rate of patients with T4a tumors with bone invasion and T4a tumors involving skin and/or lip was 33.3% and 57.1%, respec-

TABLE 3. Distribution of T-N stage

T	N0 (%)	N1 (%)	N2 (%)	Total (%)
T3 limited to buccal mucosa	5 (55.5)	2 (22.2)	2 (22.2)	9 (25)
T3 alveolar mucosa involvement	3 (37.5)	2 (25)	3 (37.5)	8 (22.2)
T4a bone invasion	6 (50)	2 (16.7)	4 (33.3)	12 (33.3)
T4a lip or skin invasion	4 (57.1)	2 (28.5)	1 (14.3)	7 (19.4)
Total	18 (50)	8 (22.2)	10 (27.8)	36

T: tumor stage; N: nodal stage

TABLE 5. Three- and 5-year disease-free survival rates of T3 and T4a tumors

T	3-year disease-free survival %	p	5-year disease-free survival %	p
T3 buccal mucosa	66.7	0.780	66.7	0.572
T3 alveolar mucosa involvement	75		50	
T4a bone invasion	50	0.732	33.3	0.397
T4a lip or skin invasion	57.1		57.1	

T: tumor stage

TABLE 4. Three- and 5-year recurrence rates of T3 and T4a tumors

		T3		T4a		Total		
		n	%	n	%	n	%	p
Three-year recurrence	Patients without recurrence	12	% 70.6	10	% 52.6	22	% 61.1	0.270
	Patients with recurrence	5	% 29.4	9	% 47.4	14	% 38.9	
Five-year recurrence	Patients without recurrence	10	% 58.8	8	% 42.1	18	% 50.0	0.317
	Patients with recurrence	7	% 41.2	11	% 57.9	18	% 50.0	

T: tumor stage; n: number of patients

tively. With regard to survival rates, no statistically significant difference was observed between T3 and T4a tumors and between the subgroups of T3 and T4a. The data are presented in Table 5.

DISCUSSION

Buccal carcinoma is a locally aggressive tumor and is associated with a poor prognosis of the high incidence of locoregional recurrence rates of 26.5%-56%, as reported in literature (1-3, 5, 6-8). The worldwide incidence of buccal carcinoma varies according to the cultural and environmental differences. There are some differences between whites and Asians, such as incidence, presenting age, and etiologic factors (1, 4). The incidence of buccal carcinoma is much higher in Asia and Taiwan because of the high prevalence of betel quid chewing (1, 7, 8). In Turkey, the major etiologic factors are cigarette and alcohol abuse, similar to European countries. This difference in the etiology may also change the prognosis particularly in advanced stage disease, as most of the tumors in the early stages can be controlled either by primary or salvage surgery.

Most of the reports in literature include every stage of buccal carcinoma regardless of extension of the tumor (1-3, 5, 7-9); hence, it is difficult to compare our results with the existing reports. Similar with our findings, the incidence of lymph node metastasis of buccal carcinoma ranged as 0%-80% for T3 tumors and 50%-63% for T4a tumors in literature (2, 3, 8).

Patients with moderately/poorly differentiated buccal carcinoma tended to present more often with N+ disease than well-differentiated tumors and had a poor survival rate (1). In contrast with previous reports, >50% of the tumors in our study were well differentiated and presented poor prognosis.

The locoregional failure rate was reported as 39.3% for patients with T1–2N0 disease treated with surgery alone (8). In our series, the locoregional control for patients with T3-T4a disease was 50% after surgery and adjuvant radiotherapy. Most recurrences in our study occurred within 2 years of primary treatment (10 [55.5%] of 18 patients), but a remarkable number of recurrences also occurred in the third year. Compared with literature, our data are within average ranges.

The 5-year disease-specific survival ranged as 31%-69% for T3 tumors and 50%-53% for T4 tumors (1, 2, 7). We observed lower survival rates particularly for T4a tumors with bone invasion. The present study confirms yet again that local recurrence is the major cause of death in particularly advanced stage oral cancer patients treated through radical surgery. All local recurrences developed at the base and edges of the flaps, infiltrated to either the pterigopalatine fossa, mandible, or pterigoid muscles and could not be diagnosed early despite a persistent clinical or radiological suspicion. Both, the presence of local flaps and fibrosis caused by radiotherapy, were the main causes of the late diagnosis of recurrence. Most of the patients refused salvage surgery and received palliative radiotherapy. Clear surgical margins could not be achieved in patients who underwent salvage surgery.

In AJCC staging, T1-3 tumors of the oral cavity are staged according to the diameter of the tumor (6). All the tumors that extended to the adjacent sides were classified as T4 tumors, but the effect of involvement of different sides on survival has not yet been examined for buccal carcinoma. Our series challenges the assumption that the involvement of the different adjacent sides portend different prognosis in advanced carcinoma of the buccal mucosa. Secondary to the low incidence of these tumors, this study is limited by a small sample size as well as by the retrospective design. The number of patients was extremely small to allow comparison of results for the involvement of all adjacent sides. The patients were divided into four groups, which mainly presented the advanced tumors limited to the buccal mucosa, tumors with invasion of adjacent mucosal sides, tumors with bone invasion, and tumors with skin invasion.

Advanced stage buccal carcinoma, even limited to buccal mucosa, has been shown to have high recurrence and low disease-free survival rates. Despite the lack of statistical significance, there seemed to be a trend toward worse survival among the patients with bone invasion. The differences in the survival, which did not have a statistical significance, could be significant if the sample size was larger. Further studies with a large number of patients are required to define the effect of involvement of different sites on prognosis.

Ethics Committee Approval: Ethics committee approval was received for this study from Ankara Oncology Training and Research Hospital (Approval No: 03.2013).

Informed Consent: Informed consent was not necessary due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - E.C., Ü.T., C.K., P.A.; Design - E.C., Ü.T., F.T., C.K.; Supervision - E.C., Ü.T., C.K.; Resource - E.C., Ü.T., C.K., P.A.; Materials - E.C., Ü.T., C.K., P.A.; Data Collection and/or Processing - E.C., Ü.T., C.K., P.A.; Analysis and/or Interpretation - E.C., Ü.T., F.T.; Literature Search - E.C., C.K.; Writing - E.C., Ü.T., C.K.; Critical Reviews - E.C., Ü.T.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Original Article

DOI: 10.5152/cjms.2018.311

3D Printing of Surgical Instruments for Children: Testing the Novel Concept

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Cite this article as: Mammadov E, Ersin A. 3D Printing of Surgical Instruments for Children: Testing the Novel Concept. Cyprus J Med Sci 2017; 2: 57-60.

BACKGROUND
Three-dimensional (3D) printing is currently being explored in various medical fields with promising results, and customized surgical instrument prototyping and production seems to be one of the promising approaches, particularly in pediatric surgery. This study aimed to test the possibility of desktop 3D printing of surgical instruments for use in pediatric surgery.

MATERIAL and METHODS
Roux retractor and infant laparoscopic trocar were designed using Solidworks 3D CAD software (Dassault Systemes, FR). Mechanical durability simulation tests were performed using Solidworks Simulation software. The instruments were printed in Ultimaker 2+ Extended 3D printer (Ultimaker, NL) using 2.85-mm polylactic acid filaments.

RESULTS
Roux retractor was designed in 15 min and printed in 90 min. Laparoscopic trocar was designed in 2 h and printed in 2 h. Application of 5-kilogram force (kgf) resulted only in 0.84-mm displacement in infant laparoscopic trocar. The 5 kgf applied to the Roux retractor's curved face caused 9.22-mm displacement. The laparoscopic trocars weighed 7.40±0.07 g, and Roux retractors weighed 12.50±0.04 g. The interior chamber of the 3D-printed laparoscopic trocars withstood a mean of 10±1.5 mmHg pressure without any obvious air leakage. Post-sterilization culture results of all prototypes were proven to be sterile.

CONCLUSION
3D printing of surgical instruments is a promising field in pediatric surgery as it offers a great versatility regarding both design and production.

Keywords: Three-dimensional printing, surgical instruments, children, pediatric surgery

INTRODUCTION

Three-dimensional (3D) printing gained widespread acceptance in many fields of industry and science. Rapid prototyping (RP) technology brought our design to real objects instantly, which allowed us to handle and modify the functional prototypes before production. Conventional manufacturing processes require complex and time-consuming molding techniques. However, RP and desktop 3D printing allow scientists to see and hold their functional prototypes in a relatively short time.

Three-dimensional printing made a quick entrance in medicine, and surgical sciences adapted this technology at the same time with the automotive engineering and aviation fields. The main applications of 3D printing in the field of surgery include manufacturing of anatomic models based on patient imaging studies, instrument, device, implant production and regenerative medicine (1-7).

Many studies have been conducted regarding organ models, prosthetics, and surgical implant manufacturing; however, few reports are available related to 3D printing of surgical instruments (8-11). To our knowledge, there is no published work

This study was presented at the 33th National Pediatric Surgery Congress, 28-31 October 2015, Antalya, Turkey.

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Received: 06.12.2017
Accepted: 02.01.2018

exploring this issue in the field of pediatric surgery. In this study, we aimed to test the possibility of manufacturing 3D printed surgical instruments for use in children.

MATERIALS and METHODS

All design and manufacturing operations were performed in university-based 3D printing facilities. Ethical approval and informed consent were not required as there were no human or animal experiments. Two types of instruments were selected; Roux retractor was chosen as the low-detail level and infant laparoscopic trocar was selected as a high-detail level instrument. The instruments were designed using Solidworks 3D CAD software (Dassault Systemes, FR). Mechanical durability simulation tests were performed using Solidworks Simulation software (Dassault Systemes, FR) prior to the printing process. During design, fine meshes were created with approximately 80,000 nodes on each instrument to obtain more realistic results from the Solidworks Simulation software. The holding nodes and force-applied nodes were chosen as per the directions of surgical use of these instruments. For a better comparison, all designed instruments were tested under same conditions with 5 kgf, which is equal to 49 Newton (N). Regarding the design of the instruments, one to three faces were chosen for applying the force (Figure 1). The applied forces were expected to create mechanical stress all over the instrument since we were looking for the most vulnerable part of our designs. Mechanical stress is a physical quantity that expresses the internal forces that neighboring particles of a continuous material exert on each other. Maximum displacement is representing areas which had the most displacement under the specified forces. Irreversible plastic deformation point is defined as the point at which material goes into a stage of inability to turn back to its original state, and this condition is followed by fracture. The glass transition of polylactic acid (PLA) occurs at 60°C, and the cooling process creates few micro-fractures, but these fractures are considered negligible. For better surface finishing, the printed instruments had five outer shells, which resulted in smoother outer surface.

Five of each instrument prototypes were printed in Ultimaker 2+ Extended fused deposition modeling (FDM) 3D printer (Ultimaker, NL) using 2.85-mm PLA filaments (Figure 2). All printed products were found to be contaminated with *Pseudomonas aeruginosa* (ATCC 27853) and placed in 5% sheep blood and Eosin Methlene-blue Lactose Sucrose Agars (EMB). After incubation at 37°C for 24 h, the contamination was proved (Figure 3) in both agars, and the products were sent to be sterilized using vaporized hydrogen peroxide. Sterilized products were placed again in agar for incubation. Each product was weighed and examined for the need of post-processing (sanding and polishing). Additionally, laparoscopic trocars were tested for air tightness using fluid immersion technique under constant pressure. The pressure was maintained and measured using manual manometer, and this test was repeated for comparison with the standard Karl Storz infant laparoscopic trocar (Karl Storz GmbH, Tuttingen, GE). Mean values and standard deviations were calculated using IBM SPSS v21 for Macintosh (IBM, VA, USA).

RESULTS

Design time varied for each instrument; Roux retractor was designed in 15 min, and laparoscopic trocar was designed in 2 h. During mechanical stress simulation test, the force per mm^2 in laparoscopic trocar resulted in 9.7kgf, and this force which is nearly double the originally applied force caused only 0.84-mm displacement in the instrument. The same force when applied to the Roux retractor's curved face resulted in 1.1 kgf/mm^2 and caused 9.22-mm displacement (Table 1). None of the instruments

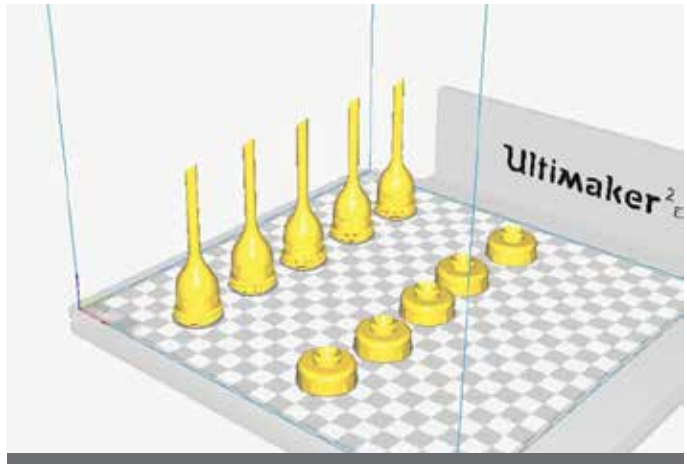

FIGURE 2. The view of five trocars on the build plate in the 3D printer slicing software

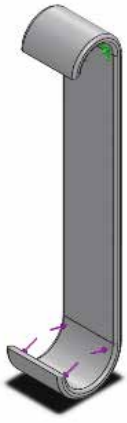

FIGURE 1. Stress simulation points in Roux retractor (Solidworks Simulation)

FIGURE 3. Contaminated laparoscopic trocar prototype in 5% sheep blood agar (note the intraluminal contamination)

reached the irreversible plastic deformation point during the simulation. The variability of the resulting forces per mm^2 was caused by the selection of the force application points to mimic the natural use direction of the instruments during the surgery and the design of the instrument itself.

Each Roux retractor was printed in 90 min, and each laparoscopic trocar was printed in 120 min. None of the final products required post-processing (Figure 4, 5). The mean weight of the printed laparoscopic trocars was 7.40±0.07 g and of Roux retractors was 12.50±0.04 g. The material cost was 43 and 51 Euro cents per piece respectively. All ten final products were found to be sterile in post-sterilization cultures. During the air leak tests, the interior chamber of the 3D printed laparoscopic trocars withstood a mean of 10±1.5 mmHg pressure without any air leakage, and this result was comparable with the original Karl Storz infant trocar which withstood 11 mmHg pressure.

DISCUSSION

Three-dimensional printing is developing very fast in the field of surgery, and this is the right time for pediatric surgeons to adopt this new technology. Till date, the most striking application of this technology is printing organ and tumor models for preoperative planning (4-6, 12). At the same time, 3D bioprinting is on the way to start a whole new era for the surgeons (13).

TABLE I. Results of stress simulation tests for the designed instruments

Part	Applied Force (kgf)	Number of Applied Faces	Resulting Maximum Stress (Kgf/mm^2)	Number of Nodes	Max. Displacement (mm)
Laparoscopic Trocar	5	3	9.7	88974	0.84
Roux Retractor	5	1	1.1	79511	9.22

* total sensitivity was calculated by the number of sensitive organisms/total organisms (47)

FIGURE 4. 3D printed laparoscopic trocar (with the inserted original Karl Storz 3-mm instrument)

FIGURE 5. 3D printed Roux retractor

Currently, there are about 15 different technologies in three dimensional printing additive manufacturing, and all of them use different methods and polymers. The most frequently used methods are FDM, stereolithography (SLA), and selective laser sintering. Among those three, the most user-friendly method is the FDM technology which utilizes the thermoplastic polymers running through a heated nozzle system and adds the molten plastic layer by layer on the printing bed. The main advantage of FDM printing is the ability to print PLA, which is an FDA-approved biocompatible, biodegradable, and environment friendly polymer (14-16).

Before manufacturing a surgical instrument from thermoplastic, we knew that it had to face competition with its stainless steel counterparts. This issue was taken into consideration; the designs were modified to be slightly thicker than the conventional stainless steel instruments and were repeatedly tested for mechanical strength in Solidworks Simulation software prior to manufacturing. The main advantage of the simulation program over the conventional stress tests was the ability to observe the exact weak points of the final product and modify the design accordingly prior to printing. The printing process started after the tests proved that the instruments were resistant to stress. The final products were strong enough to be used as disposable instruments. One of our observations was that printing the part with 100% infill created a more solid and durable instrument. This issue also increased the reliability of our simulation tests. Conventional stress tests were avoided as we noticed little displacement in the simulation, and intended use was in the field of pediatric surgery in which the surgeons do not apply excessive stress on the instruments.

The other important issue was sterilization of the products after printing. Our end products were contaminated with *P. aeruginosa*, and sterilization was performed using vaporized hydrogen peroxide, which is generally recommended for hospital grade plastic instrument sterilization. Post-sterilization culture results showed that all the products were completely sterile. We did not need to test another pathogen, and we did not perform polymerase chain reaction to detect bacterial DNA, as it is known that vaporized hydrogen peroxide has good material-penetrating sterilization characteristics (14). Some authors claim that 3D printed instruments can be directly printed in operation room and used without need of sterilization due to high temperatures during printing (210°C-215 °C) (8). In theory, this approach seems to be reasonable but we do not advise it until more studies are conducted.

Retractors were produced and easily tested during our study. Laparoscopic infant trocar production was more challenging due to required strength and air tightness. As we did not have possibility to print the rubber leaflet valves which prevent air leak in te trocar, we designed the trocar cap to fit the original Karl Storz (Karl Storz GmbH, Tuttingen, GE) leaflet valves and used the original valves. Interior chamber of printed trocars sustained considerable pressure with the conventional infant

laparoscopic trocar. Besides that, to increase air tightness, we plan to print the leaflets with new flexible PLA or thermoplastic polyurethane filaments in near future.

Three-dimensional printing still has challenges to overcome, but the advantages it offers encourage us to carry on with research and development in this field. The most obvious disadvantage is longer production time compared to the conventional fabrication process. Another drawback is the scarcity of FDA-approved polymers for 3D printing. The concept of 3D printing is about rapid production of functional prototypes than mass production.

The major limitation of our study was the lack of animal or human experiments. We plan to overcome this issue as soon as porcine models are available in our animal test laboratory. The other limitation was that we have only designed and printed two types of instruments, so it is impossible to generalize and apply our results to the whole set of surgical instruments. However, we think that our preliminary study showed promising results, and this urges us to continue research.

Three-dimensional printing of surgical instruments has benefits for low-income countries and far rural areas. In addition, this method can be used in military and aerospace missions where instead of carrying loads of instruments, one can just place a computer loaded with designs and several 3D printers. For pediatric surgeons, the most obvious advantage is the ability to modify and scale the instruments to the patient's size and the ability to produce dedicated instruments for special surgical cases particularly for neonatal congenital conditions.

Three-dimensional printing of surgical instruments for children deserves to be studied and developed as it offers the possibility to produce customized and scalable equipment for use in pediatric surgery.

Ethics Committee Approval: N/A.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.M., E.A.; Design - E.M., E.A.; Supervision - E.M.; Resource - E.M., E.A.; Materials - E.M., E.A.; Data Collection and/or Processing - E.A.; Analysis and/or Interpretation - E.M., E.A.; Literature Search - E.M.; Writing - E.M., E.A.; Critical Reviews - E.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Review

DOI: 10.5152/cjms.2018.295

Occupational Burnout in Healthcare Workers

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Cite this article as: Yaman H, Occupational Burnout in Healthcare Workers. Cyprus J Med Sci 2017; 2: 61-3.

Depression, burnout, and psychosomatic disease evolve owing to chronic stress due to the profession of healthcare workers. The diagnosis and management of burnout is a challenge. Although burnout is similar to depression, it fails to meet any of the latter's diagnostic criteria. The affected individual might commit suicide if not appropriately managed. Interventions to the individual might have, besides institutional improvements by the inclusion of the institutional management to process, beneficial effects on the prevention of burnout.

Keywords: Burnout, depression, profession, stress

INTRODUCTION

Healthcare workers develop chronic stress, depression, burnout, or psychosomatic illnesses owing to the stress they are subjected to due to their work or occupation (1, 2). Among the abovementioned problems, the concept of burnout has become quite a popular one. This term has been specially suggested by Schaufeli et al. (3) for individuals having different sub-dimensions (exhaustion, depersonalization, and personal success). Burnout was first introduced by Freudenberger in the 1970s. Freudenberger, who is basically a psychotherapist, observed that doctors who struggled with drugs were deprived of time and depressed. After thoroughly studying the situation, he stated that other occupational groups were affected by this situation too (4).

Among individuals with burnout, Schaufeli et al. (3) identified conditions such as exhaustion, fatigue, excitement and loss of enthusiasm, feelings of inadequacy, frustration, cynicism or inefficiency, and dysfunctional behaviors, which develop at the workplace (5).

In addition to this, the problem is also responsible for alienation, sickness-leave, resignation, or intensive workplace change. Among those who do not resign, a decrease in job productivity and efficiency, job satisfaction, and loyalty to work and organization in the exhausted employees is observed. Somatic and concrete disease-promoting effects of burnout are also observed to occur (e.g., depression, musculoskeletal pain, type 2 diabetes, cardiovascular disease, cognitive problems, and premature mortality) (6).

Although burnout is reported to cause concrete somatic problems, it is generally not considered a clinical entity. It is mostly expressed as psychological distress and a psychosocial problem (3, 5).

Schaufeli et al. (3) have proposed the term "engagement" to save the concept of burnout from the negative burden. "Affinity" is defined by sub-dimensions such as energy, participation, and effectiveness. It is preferable to use more positive expressions than terms such as burnout, cynicism, or disability.

PATHOGENESIS

The development of burnout is explained by a stress model. According to the model, stress is actually a protective reaction that protects the individual against a sudden and unexpected attack. However, in the case of a persistent state of stress, the individual remains unresponsive to the incoming influences, is blunted, and is exhausted. Exhaustion is not equal in every individual. For example, particularly, those who are easily accountable for and enthusiastic toward or integrated with their work more easily develop burnout. People who work in the service sector are more affected (i.e., teachers, lawyers, engineers, police, guards, etc.) (5, 7). It is possible to include healthcare workers, particularly family physicians, in this group (8, 9).

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Received: 17.11.2017
Accepted: 18.11.2017

RISK FACTORS

Maslach et al. (6) describe six risk factors that play a role in the development of burnout: incompatibility at work, incompatibility in job control, lack of awards, feeling of not being in a positive relationship with others in the workplace, perceptions of fair treatment, and conflicts between values. In addition, workload and time pressure, role conflict and confusion, lack of social support, lack of feedback, loss of autonomy, and lack of participation in decision making are considered as risk factors. On an institutional level, work autonomy, job security, personnel participation, work culture (participation, equity, and justice), and programs for mental health of employees influence burnout development (10).

Because of their work, during the development of burnout, individuals neglect the social environment, family experiences, and personal health. The level of the individual's job and self-control can be particularly decisive. As exhaustion deepens, the efficiency and efficacy of the individual's work gradually decreases. As mental concentration, creativity, and cognitive functions diminish, their memory also weakens. The number of mistakes in their work starts to increase, and they start to blame themselves and others unless they succeed. It is possible for them to experience day-to-day torture due to the intense stress they experience within them, dissatisfaction with themselves, anxiety, lack of courage, and mistakes they make. It is sometimes possible to find remedy in alcohol and substances (7).

DEVELOPMENTAL STAGES

When we examine this process in terms of the developmental stages of burnout described by Freudenberger and North, we could divide this process into 12 phases. Stages are not necessarily in pursuit of something. Sometimes it is possible for different phases to coexist (Table 1) (7).

DIAGNOSIS

Despite the emergence of somatic complaints as well as behavioral problems, burnout remains a problem in Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition V (11). In this moment it could be expressed as a somatoform disorder, whick could not be classified. In the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10), it is expressed under the heading "Problems related to life management difficulty " (Z73) (7, 12). However, in some countries (Sweden and the Netherlands), burnout is treated as a medical diagnosis (3).

The Maslach Burnout Scale is the most commonly used measure of burnout, although there is no exact scale for burnout. This scale divides the phenomenon of burnout into three sub-dimensions: exhaustion, depersonalization, and personal accomplishment. Some researchers have stated that the main element of exhaustion is the exhaustion sub-dimension (3). On the other hand, increasing evidence suggests that exhaustion is similar to depression (13). However, it is also emphasized that this overlap should be confirmed by other studies. It covers the psychosocial dimension of depression. Rather than a psychiatric or clinical situation, it is a psychosocial condition (14).

MANAGEMENT

The treatment of exhaustion in individuals is difficult because all individuals react in different ways. If the employer does not have control over the stressors of the employees of the institution, it will be difficult to manage the exhaustion of employees. Studies have shown that situational and institutional factors play a greater role than individual factors. Exhaustion, cynicism, or professional activity can be treated more easily. Cynicism and professional activity were found to be more resistant to treatment (6).

When evidence-based reports were examined, it was found that interventions to reduce complaints, burnout, and work-related stress were more successful at both individual and small group levels. The level of achievement was moderate (10).

Smaller programs have also provided positive stress relief. Staff training and workshops have been shown to be successful in avoiding burnout complaints. It is possible to include awareness trainings on stress-related issues. Particularly, it has been argued that intervention may be more successful if staff develops perception that the environment is safe and not threatening (15).

TABLE I. Different phases of burnout

1. Trying to self-assert yourself: Compulsive self-initiative begins at work.	2. More work: To prove themselves to others or to the institution they work, they dedicate themselves totally to work. They try to do everything themselves.	3. Ignoring their needs: There is no time and energy for things other than work. Family, friends, nutrition, sleep, etc. These are neglected.
4. Avoiding conflicts: They realize that something is wrong, but they cannot produce a solution. They have a crisis within themselves. Solving the problem does not work. The first somatic complaint may arise.	5. Passing values in favor of the business: Focus only on work, emotional blunting starts. No time for anyone except work.	6. Disbelief is a new challenge: Dislike of things around and work together, increased cynicism and aggression, believe that the increasing problems were caused by lack of time, they do not see their change as a cause of this problem.
7. Move away: They isolate themselves. Hopelessness and irregularities begin. Take refuge in alcohol.	8. Possible behavioral change: A person who is alive and involved once becomes increasingly shy, fearful, and apathetic. The sense of worthlessness increases. People around them can not ignore the behavioral changes in the person.	9. Depersonalization: The irritation is cut off by themselves. They see neither themselves nor others as precious. They can not perceive their own needs. Life becomes mechanical.
10. Inner space: They grow desperately and act helplessly to fill the gap. Excessive sexuality, nutrition, drug or alcohol use. Free time is dead time.	11. Depression: An overly busy person becomes desperate and exhausted. No future expectations. There are concrete depressive symptoms. Ex. Agitation, apathy, the meaninglessness of life.	12. Burnout syndrome: Suicidal thoughts arise in order to avoid them. Some people commit suicide. They experience mental and physical depression. They need urgent medical support.

Cognitive behavioral therapies, particularly at the individual level, have shown modest positive effects on relaxation and meditation. In general, interventions aimed at individuals have been shown to be moderately successful (10). In addition to this, prevention of burnout could be provided by starting with relaxation exercises in the sun, eating healthy, being involved in sports, sleeping well, drawing limits, taking breaks in technology, improving creativity, and learning to cope with stress.

Studies including institutions have been rarely found (10). In one study, however, institutional interventions were claimed to have a longer effect (16). Prevention of burnout is possible only through institutional improvements and individual training. More importantly, effectiveness will be enhanced, especially in the presence of support by the institution (10). In the development of burnout, institutional problems related to imbalance of workload, control, reward, community, justice, and values are held responsible. Reducing workload by providing employees with enough rest and determining clear values in which employees of the institution may be involved, support of the working community by leaders and managers and the establishment of good relations with employees are recommended. Equitable management approach also relieves the employees. The rest of the workers' troubles caused a decrease in the level of burnout (6, 17).

CONCLUSION

Burnout is sneaky and management is a very difficult disease. Although it is expressed as being similar to depression, it still has no clinical diagnostic feature. If diagnosed and not timely intervened, it is a question that can lead to different clinical morbidity and mortality as well as depression and suicide. Although interventions have shown effect at the individual level, it might be possible to create positive effects by incorporating institutional improvements and, in particularly, by the involvement of the management into this process.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Review

DOI: 10.5152/cjms.2018.288

Brain Death and Importance of Preserving Organs of Brain-Dead Donors in Intensive Care Unit

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Cite this article as: Taşargök Ö, Deniz F, Çelik O, Serger N, Koç M, Bedevi R, et al. Brain Death and Importance of Preserving Organs of Brain-Dead Donors in Intensive Care Unit. Cyprus J Med Sci 2017; 2: 64-6.

Nowadays, due to an increasing number of patients waiting for organ transplant, the diagnosis of brain death in the intensive care unit has become important. Anesthesiologists and intensive care specialists have important responsibilities when diagnosing brain death. In this paper, legislation in our country, the diagnostic criteria for brain death, and donor protection will be discussed.

Keywords: Brain dead, donor, intensive care unite

LEGISLATIONS OF TURKISH REPUBLIC OF NORTHERN CYPRUS (TRNC)

Brain death was defined by two French neurologists who first described the concept in 1959 by detecting irreversible brain damage in 23 patients. Since then, the patients who are diagnosed as brain dead are considered to be the most important factors in terms of giving hope to other patients undergoing treatment for organ failure and waiting for organ transplant.

The laws concerning organ transplant in our country, which comprise the "Human Cell, Tissue and Organ Transplant Related Rules Regulating Act," were passed on October 27, 2014 by the Assembly of TRNC (1). On May 2, 2016, in addition to this law, the diagnostic criteria for brain death were published in the Official Gazette No. 269 (2).

According to this law, a neurologist, a neurosurgeon, and an anesthesiologist decide if brain death has occurred following the rules of evidence-based medicine.

DIAGNOSIS OF BRAIN DEATH BY ORGAN REGULATION AND TISSUE TRANSPLANT SERVICES IN TRNC

Brain death is a clinical diagnosis that can be described as the irreversible and complete loss of all brain functions.

[1] Prerequisites for the diagnosis of brain death are as follows:
   a) Determining the cause of coma
   b) Determining that the brain damage is widespread and irreversible
   c) Core body temperature ≥32°C
   d) Absence of hypotensive shock
   e) Exclusion of intoxication and the effects of some drugs that can cause reversible coma
   f) Absence of metabolic, electrolyte, and acid–base disturbances that can explain the clinical picture independently

[2] The following points are to be considered in the diagnosis of brain death if all the conditions listed under Item I above are identified:
   a) Being in the state of deep coma (full unresponsiveness)
   b) Absence of brain stem reflexes:
   · Pupils are unresponsive to bright light, fixed in a midsize or dilated position (4–9 mm)
   · Absence of oculocephalic and oculovestibular reflexes in the eyes during the examination

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Received: 30.10.2017
Accepted: 18.12.2017

- Absence of corneal reflex
- Absence of tracheal and pharyngeal reflex

c) Absence of spontaneous breathing efforts and having a positive apnea test.

[3] For an apnea test to be performed, the following prerequisites must be satisfied: normothermia, normotension, and normovolemia. Under these conditions with appropriate mechanical ventilation, the patient's $PaCO_2$ level has to be increased above 35-45 mmHg and PaO_2 level has to be increased above 200 mmHg. Once these conditions are met, intratracheal oxygen should be administered to the patient after disconnecting from mechanical ventilation. At the end of the test, if spontaneous breathing does not occur despite the $PaCO_2$ levels being ≥60 mmHg or rising by 20 mmHg or more compared with the baseline, the apnea test is considered to be positive. [4] In medical conditions such as pneumomediastinum and pneumothorax, where it is not possible to conduct the apnea testing, a supporting test specified by the physician is performed to evaluate if the brain circulation has stopped. If the test results are consistent with the diagnosis of brain death, the confirmation of brain death is complete.

[5] The following findings do not pose an obstacle to the diagnosis of brain death:
a) Detecting deep tendon reflexes
b) Detecting superficial reflexes
c) Presence of Babinski sign
d) Presence of spinal reflexes and automatisms
e) Presence of sweating, flushing, fever, and tachycardia
f) Absence of diabetes insipidus

[6] In cases where brain death was diagnosed
a) The clinical table is formed upon the first neurological examination where the diagnosis of brain death was confirmed; it was observed that the diagnosis remained unchanged in the second neurological examination performed on newborns (younger than 2 months) after 48 hours, children (aged between 2 months and 1 year) after 24 hours, and children (older than 1 year) and adults after 12 hours and in case of anoxic brain deaths, after 24 hours.
b) The diagnosis is confirmed with two supporting tests performed on the newborns (younger than 2 months) and 2-month-old infants and a laboratory method deemed suitable by the physicians' board for patients older than 2 months.
c) It is mandatory to perform a supportive clinical test (computed tomography angiography of brain), which would evaluate the cerebral circulation.

Diagnostic criteria around the world have shown little change. The most distinct differences among countries can be identified as the lack of mandatory confirmatory diagnostic tests and the number of specialist doctors (3, 4). Unlike other countries, in the United Kingdom, the irreversible loss of brain stem functions only is enough to confirm brain death.

After the conditions written above are fulfilled, the relatives of patients are reported that patient's brain death has occurred. The family consent ranges between 30% and 40% around the world (5).

Globally, Spain has the highest donor rate with 33-35 donors per million people. According to Turkey's data, 594 brain deaths have been reported in 2007, 245 of which were donors (41% acceptance rate), and 720 brain deaths have been reported in 2008, of which only 262 were donors (36% acceptance rate).

In TRNC, 6 brain deaths have been reported in 4 months, and 4 of these were donors (66.6% acceptance rate).

Some data show that the main reason for rejection of organ donation by patients' families is the religious factor. According to a study conducted in Saudi Arabia, the acceptance rate of families was reported as 17%. This rate was higher than the rates reported in 1982, but it has gradually decreased in the early 2000s. Recent fatwas against organ donation given by some religious leaders are considered as the reason behind the rate decrease. Therefore, it would be beneficial for clergymen to be directed to contribute to organ donation.

The media's influence on public awareness is significantly high. If the power of the media focuses on organ donation, with the help of more comprehensive, effective, and motivating broadcasts, the donation rate can increase.

In this regard, it is very important for the Ministry of Health, the Public Health Department, and hospital authorities to show the necessary management and to shape the society.

After the family or relatives give their permission for the organs of the patient whose brain death is verified to be used for transplantation, the patient automatically becomes a donor.

DONOR CARE IN THE INTENSIVE CARE UNIT

Cardiovascular Changes and Cardiovascular Support

Due to cerebral ischemia and an increased intracranial pressure, vasomotor control is lost, and levels of circulating catecholamines increase. This period is called "catecholamine storm." Hypertension, tachycardia, and increase in cardiac output occur. This phase is followed by the cardiovascular collapse phase. The loss of sympathetic activity and decreased systemic vascular resistance cause hypotension and bradycardia (6). The aim of treatment for the cardiovascular system is to meet the metabolic needs of the body and to prevent organ ischemia. Hemodynamic targets are defined using the rule of 100s: systolic blood pressure level >100 mmHg (mean arterial pressure >65 mmHg), heart rate level <100 beats/min, urine output >100 mL/h, hematocrit >30%, pO_2 >100 mmHg, and central venous pressure >10 mmHg. To achieve the rule of 100s while treating the target, central venous catheters, pulmonary artery catheter, and echocardiography can be used. Fluid management is performed using crystalloid and colloid fluids. If deemed necessary, a blood transfusion can be applied to the patient using positive inotropic agents.

Pulmonary Changes and Pulmonary Support

Aspiration pneumonia, lung damage, and neurogenic pulmonary edema due to pulmonary complications often develop.

The goal of treatment is applying mechanical ventilation and providing normocapnia and normoxia. In addition, appropriate treatment should be initiated if lung infection is developed (7).

Changes in the Endocrine System and Endocrine Support

Due to the brain stem death, hypothermia can develop significantly because of the primary temperature control center being affected depending on level of damage in the hypothalamus. Patients' body temperature should immediately be increased and maintained at a normal or near-normal temperature. For this purpose, heating blanket should be used, the ambient temperature should be increased, and the inhaled gas and intravenous fluids must be heated.

One of the most common problems, which develop due to the lack of antidiuretic hormone released from the posterior lobe of pituitary gland, is diabetes insipidus. In this case, polyurea occurs, and urine output increases (>4 ml/kg/hour). Urine specific gravity is generally lower than 1005. Accordingly, hypovolemia, hyperosmolarity, hyponatremia, hyperkalemia, and hypocalcemia can be observed. During the treatment, fluid replacement should be performed with hypotonic solution, tap water should be provided via nasogastric routes, and/or urine output of 1–2 ml/hr should be kept at normal levels. In severe cases, despite the fluid replacement that has been applied, biochemical analysis values of the patient may not be adequately balanced. In this case, desmopressin acetate 2–4 mmg/day may be given (8). Affected by the anterior pituitary gland, cortisol, insulin, and thyroid hormones decrease. When a decrease occurs in the insulin levels, increased anaerobic metabolism and acidosis occur. In this case, if hyperglycemia is detected, the patient is given insulin intravenously, and blood glucose levels must be kept lower than 200 mg/dL.

CONCLUSION

As a result, to increase the rate of organ donation in our country, patients that may be potential donors should be identified. Specific tests must be conducted as soon as possible on the patients that are suspected to be brain dead, and the diagnosis must be verified quickly and accurately. Necessarily, there should be a meeting between donor's family and an experienced and trained transplant coordinator. After donor candidates are determined, organs must be well protected, and body functions must be maintained in a normal state until the organ transplantation is complete. Transplantation depends entirely on the supply of viable organs for implantation. There is a significant imbalance between the number of available organs and potential recipients. In the US and European transplant centers, the number of potential transplant recipients has increased to more than 133,000, yet the number of donated organs is not increasing sufficiently (9-11). For this reason, donors should be cared for by experienced teams in the intensive care unit. If all these steps are successfully performed, the number of donors will increase in our country as well.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - Ö.T., F.D., O.Ç.; Design - M.K., N.S., D.O.; Supervision - F.D., Ö.T., O.Ç.; Resource - M.K., N.S., D.O.; Materials - Ş.O., R.B., M.K.; Data Collection and/or Processing - F.D., Ö.T., O.Ç.; Analysis and/or Interpretation - M.K., N.S., D.O.; Literature Search - M.K., N.S., D.O.; Writing - Ö.T., Ş.O., R.B.; Critical Reviews - Ş.O., R.B., N.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Review

DOI: 10.5152/cjms.2018.233

Sudden Cardiac Death in Athletes: Tips for Prevention

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Cite this article as: Yaman H, Akçay İ, Günay G. Sudden Cardiac Death in Athletes: Tips for Prevention. Cyprus J Med Sci 2017; 2: 67-71.

In Turkey, an increase in the number of people interested in running and particularly, in those participating in marathons is quite striking. The age of participants is increasing as well. Nowadays master athletes are often seen in these competitions. Although the benefits of sports are not open to debate, sports events, such as marathons, pose potential risks to participants. Pre-participation evaluations are important as well as follow-ups by a coach for individuals participating in sports to minimize the damage that this paradox can create. Sudden cardiac death (SCD) is the most feared and dramatic situation during organized sports events. Although it is not very common, describing the inflicted trauma is not quite possible. In this review, medical evaluations on adult and elderly athletes, in particular, will be discussed. Coronary artery disease, particularly in this risk group, is the leading cause of SCD. We would like to suggest a three-step evaluation of athletes in this age group. This approach seems to be relatively easy to implement considering its cost effectiveness, and it also helps identifying as many at-risk athletes as possible. Furthermore, we want to emphasize that the regulation of the emergency field of the race environment is very effective in reducing mortality.

Keywords: Sudden cardiac death, cardiac arrest, sports, athletes, acute coronary syndrome, running

INTRODUCTION

In recent years, there has been an increase in the number of individuals participating in a marathon. Whether young or old, they all want to participate in a marathon to prove themselves (1). Along with the aging population, a significant number of individuals are playing sports in their free time. For example, in the United States, 20 million individuals participate in the run every year. More than half of the participants are male and older than 35 years. Among the factors that motivate participation, which has been on the rise for the last 15 years, are the positive health effects of these activities (2). In addition to the psychological effects that the run will provide, there are also positive physical health effects. However, potential harmful effects of a full marathon are also likely to outweigh the benefits. Athletes who take this job seriously also need to prepare themselves for this activity (1). However, it is possible for us to mention a paradox related to sports. Some individuals have sudden cardiac death (SCD) caused by certain underlying structural heart problems, which is often linked to their immobility. In particular, middle-aged and elderly individuals are more susceptible to SCD. SCD due to sports needs further investigation, and it comprises 5%-6% of all SCDs (2).

The prevalence of SCD in sportsmen is 1 in 50,000/year (3). Most of the cases are observed in males (3, 4). Discussed in more detail, the frequency varies from 1 in 200,000-1 in 7,500. This accounts for occasional runners (1/750-18,000) and for marathon runners (1/50-200,000). Majority of the events occur during the half-marathon or marathon, and they mainly take place toward the end of the run (5).

If we evaluate the frequency of the occurrence of SCD in marathon runners according to the duration of the exposure, it would be possible to say that the frequency is very low. The number of deaths in marathons is 1 in 215,000 h, while in non-competitive live sport events, this number is 1 in 396,000 h; in Nordic skiing, it is 1 in 607,000 h (6).

If we were to compare these values with those in healthy individuals, it is possible to see that the risk of SCD is 56 times higher in inactive individuals. For individuals participating in sports on regular basis, this risk is five times higher. On the other hand, mild to moderate participation in sports reduces the risk of SCD by 7-10 times and the risk of myocardial infarction (MI) by 50 times. Even daily runs in moderate levels (5-10 min, <6 mil/min) have significant benefits against mortality (2).

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Received: 28.07.2017
Accepted: 26.12.2017

Middle-aged and elderly athletes (age>35 years) will be reviewed in this study. Athletes above 35 years are also called master athletes.

Sudden cardiac arrest and SCD are the sudden halt of cardiac activity and hemodynamic collapse occurring with ventricular tachycardia/fibrillation. Although hypertrophic cardiomyopathy (HCM) is more common in young people, it occurs in the elderly because of structural heart diseases, such as coronary heart disease (CAD), that have developed previously. Whether the outcome is fatal or nonfatal (after a successful cardiopulmonary resuscitation), the state of developing complaints within an hour and the absence of trauma is called SCD (7-9).

In a cumulative of 30-year study, only 4 out of 215,000 marathon runners were diagnosed with SCD. None of them complained during training or before the marathon. Three of them had no complaints before collapsing to the ground. Two of them had completed three marathons before and the other two had participated in their first marathon. Also three of the patients were diagnosed with CAD, but none had structural heart disease (10).

Structural heart diseases are at the forefront, if we closely examine SCD in sports. Tachyarrhythmia may occur at sites of abnormal myocardium or fibrotic tissue. Over time, tachyarrhythmias that develop with re-entrant arrhythmias develop into bradyarrhythmia or asystoles and cause heart blocks. Another reason is the dissection of the great vessels developing in Marfan syndrome. The causes of death in young athletes vary even according to the regions in which they live. CAD is considered to be one of the most common causes observed among athletes aged >35 years (6).

The mechanism of SCD due to CAD could not be fully understood even the process resulted to ischemic ventricular arrhythmia. Among possible mechanisms are sympathetic activation (which leads to vulnerable myocardial ischemia and thus, arrhythmia), electrolyte-related and metabolic factors (long runs may create imbalance, and most deaths occur in the last quarter of marathon, which might be caused by a heat-stroke), hemodynamic effects of hemostatic system activation, and vulnerable coronary plaques (plaque ruptures, hemostasis, and thrombosis) (2).

In nonstructural heart diseases, mostly heritable rhythm disorders (e.g., long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia) are considered to be responsible. In structurally normal hearts, arrhythmia arises because of trauma or is idiopathic. For example, Commotio cordis emerges because of a blow to the chest. Cardiac hypertrophy or myocarditis was found in the autopsy when a cause could not be detected in idiopathic cases. Also, the use of androgens for doping purposes should not be overlooked (6, 7).

Even though the use of doping in master athletes is not expected, accidental use still occurs. In particular, it is possible to mention three different agents, which have negative effects on the heart and circulatory system. These are androgens, growth factor (GF), and erythropoietin. The effects of various agents are shown in Table I (11, 12).

Different considerations have been made while screening for the condition that causes SCD. When attempting to detect structural abnormalities in the scans, difficulties are encountered for idiopathic cases (6).

Although pre-accession assessment in sports is routinely performed in many countries, its variations still exist. In some countries, only anamnesis is performed without the need for ECG, whereas in other countries, ECG is routinely assessed at scans. However, some countries, such as Denmark, do not perform scans during sports because of the low incidence of SCD (13).

It is obvious that millions of athletes must be screened. However, the incidence of congenital heart diseases in the athletic population is between 0.2% and 0.3%. In rare cases, false positivity is significantly higher. In this scope, one needs 499 extra screenings to detect hypertrophic cardiomyopathy, occurring once in every 500 athletes. This situation will result in specific costs in addition to the workload to the health system (6).

Taking into account similar findings, guides that suggest screening of young athletes have been developed. While the American Heart Association (AHA) recommends a scan solely based on anamnesis and physical examination, the European Heart Association (ESC) additionally recommends ECG (14).

In a study conducted in our country, it was understood that a questionnaire form and physical examination can give successful results during athlete examinations (15). According to the circulation of the Ministry of Health of the Republic of Turkey numbered 2014/29, dated September 24, 2014, and the circulation of the Ministry of Youth and Sports numbered 2014/12523, dated November 14, 2014, the use of Annex 6 Form is recommended for athletes' examination report. The questions in Annex 6 Form match certain questions in the guide.

In 2001, AHA published some recommendations for this risk group (Master Athletes, Athletes 35 and oved) (6, 16). Accordingly, 12 points should be taken into account during a complete anamnesis and physical examination.

TABLE I. The effects of sports efficiency-promoting agents on the heart (12)

Substance	HT	Arrhythmias	LVH	CHD	MI	CHF	SCD
Anabolic Androgens	+	+	+	+	+	+	+
HCG		+	+			+	+
Erythropoietin	+					+	
β_2 agonist		+			+	+	+
Diuretics		+					
Amphetamine	+	+			+	+	+
Cocaine	+	+		+	+	+	+
Ephedrine	+	+		+	+		+
Narcotics							+
Cannabinoids		+			+		+
Glucocorticoids	+			+			
Alcohol	+	+			+	+	+

* total sensitivity was calculated by the number of sensitive organisms/total organisms (47)

Those with a mid-high-level of cardiovascular risk profile should undergo the exercise stress test. Risk profile for males aged >40 years and females aged >50 years or those postmenopausal include having one or more risk factors such as hypercholesterolemia or dyslipidemia, hypertension, cigarette smoking, DM, MI narcosis, or loss of first-degree relative < 60 years.

An overload stress test may also be performed irrespective of other risk factors in patients with CAD history or those aged ≥65 years. There is a limited contribution of ECG to examinations in terms of CAD. However, it could help in athletes over 40 years to detect a previous MI or hypertrophic cardiomyopathy or other rare rhythm disorders.

Echocardiography is engaged in the second phase of the diagnostic process (6, 17, 18).

Asymptomatic athletes have been mentioned above. Early signs of SCD are also worth mentioning.

In particular, those who do not survive SCD are reported to be asymptomatic in general before the event. Survivors do not remember complaints before the competition because of post-resuscitation amnesia (7).

In a community-based study from 2002 to 2012, it was found that 430 (51%) of 839 cases had stimulant complaints of SCD beginning four weeks ago (19).

It has been reported that 80% of the cases complained approximately an hour before the marathon and 34% complained approximately a day (24h) before the marathon. Chest pain (46%) and dyspnea (18%) were among the most frequently reported complaints. Therefore, athletes who have developed symptoms recently should be careful and use necessary medical services (7).

Risk factors of SCD are similar to those of CAD. In addition, psychosocial factors, such as CRP elevation, excessive alcohol consumption, and stress, increase the risk, whereas long-chain n-3 polyunsaturated fatty acids reduce the risk (6, 7).

In general, positive effects of sports on health are well-known, but it is also known that loadings exceeding 11 MET-h/week have no health benefits (20).

In addition, loading-related cardiac troponin elevations, myocardial fibrosis, cardiac dysfunction, arrhythmias, coronary artery calcifications, and increased cardiovascular morbidity and mortality have been reported at high levels (20). However, in runners, troponin elevations are thought to be physiologically independent of ischemia (21). Cardiac dysfunction is mild and disappears 48 h after the loading (22). The issue of the development of atrial fibrillation risk in sportsmen is controversial. It is understood that there is a U-type risk increase for the development of atrial fibrillation. While low and high loads develop atrial fibrillation, moderate loads impede the development of atrial (23). In spite of positive effects of regular running, it was observed that coronary calcification scores are high even in marathon runners (24). Nevertheless, it is debated that findings on the effects of extreme sports on increased cardiovascular disease risk are not mature yet (20).

A review on the approach of master athletes by Chugh et al. (2) is presented in Figure 1.

CAD is an important risk factor in terms of SCD in master athletes (25). In this respect, the following points should be considered for high-risk athletes, within the framework of the proposals of AHA, American Sports Medicine College, and European Cardiovascular Rehabilitation Association Guidelines (25):

a. Risk of CAD in 10 years (Framingham Risk Score)
b. Total cholesterol level > 320 mg/dl or LDL-cholesterol > 240 mg/dL
c. DM with microalbuminuria
d. A family history of SCD or early CAD in first-degree relatives (aged < 50 years)
e. Body mass index > 28 kg/m^2

Warning signs suggested for young athletes, but which are also valid for master athletes, are presented below (26, 27):

a. Chest pain or discomfort with loading
b. Disproportionate dyspnea with loading, unexplained dyspnea, or fatigue due to loading
c. Palpitation
d. A syncope or close syncope, particularly due to loading
e. Hypertension history
f. Presence of a known cardiac murmur
g. Personal or family unexplained drowning or traffic accident
h. Family history of SCD

If we address the three-staged scanning method (Figure 1, 2) in detail, the risk assessment is primarily done in the first step. Risk factors mentioned above are taken into consideration. In our country, the Annex Form 6, which the Ministry of Health and the Ministry of Sports has suggested to family physicians, mostly contains these questions. The second stage of the evaluation is conducted subsequently for the athlete who has a positive result for risk assessment. Here a detailed clinical history is taken:

- Family history and backgrounds are handled. A positive response in terms of MI, cardiac surgery, cardiac catheterization, PTCA, pacemakers, heart valve disease, heart failure, heart transplantation, and congenital heart disease are to be considered.
- A more detailed medical examination is required for complaints, such as chest discomfort due to loading, unreasonable shortness of breath, dizziness, blackouts or taking heart medications, and not being able to find an explanation for other complaints (e.g., muscle pain)

If two of the following cardiovascular risk factors are present, then a more detailed medical examination is needed:

- >45-years-old male
- >55-years-old female, those with a history of hysterectomy, or those who are menopausal smoking history
- Blood pressure > 140/90 mmHg
- Blood pressure unknown
- Cholesterol > 240 mg/dL
- Having a first-degree male relative < 55-years-old or female relative < 65-years-old who has had MI previously

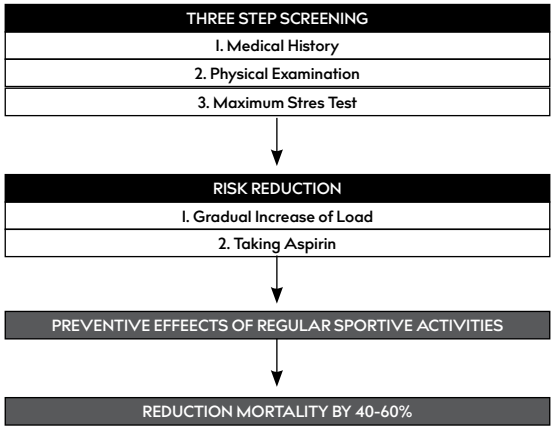

FIGURE I. Balance between SCD Risk and Benefits of Sports (2)
SCD: sudden cardiac death

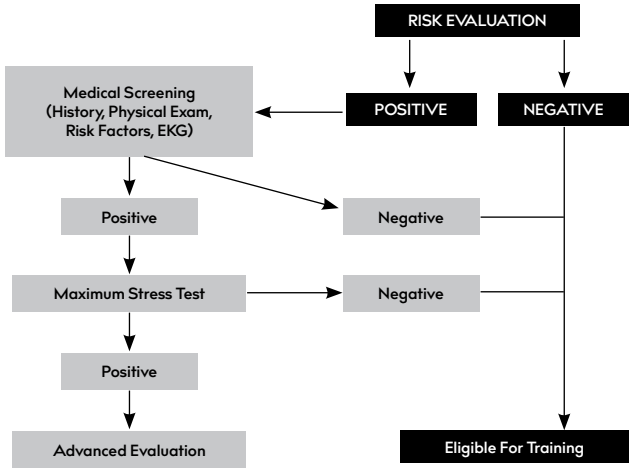

FIGURE 2. Evaluation Algorithm of Master Athletes in Terms of CAD Disease (Three-Step Scanning) (2, 28)
CAD: coronary heart disease

- Having diabetes or using medication for diabetes
- Inactive lifestyle (physical activity for >30 min/3 days/week)

If there are no positive responses to the above questions, the athlete may start training immediately (2, 28).

Detailed physical examination and a 10-year absolute CAD risk are calculated. The risks expressed in Figure I are also studied. The following suggestions are recommended according to Chugh et al. (2):

- Peak loading test must be performed if there is a high risk. If this is not possible, single photon emission CT or stress echocardiography should be performed. This is particularly for individuals with a capacity of <2 MET-h/week.
- Routine stress testing in healthy athletes is not recommended. The use of ECG and echocardiography in accordance with the requirements in addition to the examination will lead to the emergence of previously unknown or unexplained structural heart problems.
- On the other hand, the effort test is not sufficient for revealing subclinical CAD. Plaque ruptures causing SCD are caused by tightness of non-critical stenosis. Because of this, radiodiagnostic imaging of plaques is important, but it is not possible to put them into practice in terms of cost effectiveness.
- Reducing risks of elderly athletes is as important as health screenings. Slow and gradual training of beginner athletes will increase safety.
- If hypercholesterolemia is present, it is treated according to standard treatment regimens.
- The use of low-dose acetylsalicylate (75-100 mg) is recommended.

In conclusion, it is a fact that the risk of SCOR due to spore in elderly athletes is increased. As the population increases, the population at risk will also increase.

CAD is the leading cause of SCD. Among athletes who participate in sports, those who are new or less trained are particularly at risk of SCD. For this reason, master athletes as well as those with lesser training, particularly in challenging conditions, must be subjected to a three-staged scanning program. Even the three-step screening covers several guides, its validity and reliability should be determed with extensive studies (2). It is not easy to predict the risk of plaque rupture, and this group should detected in collaboration with a cardiologist by using a cost-effective approach. The use of acetylsalicylic acid before the race is promising to reduce the lethality of SCD during the competition (29). Apart from this, bystander CPR practices might be useful during marathon runs (1).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - H.Y., İ.A., G.G.; Literature Search - H.Y., İ.A., G.G.; Writing - H.Y., İ.A., G.G.; Critical Reviews - H.Y., İ.A., G.G.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Case Report

DOI: 10.5152/cjms.2017.274

Safe Anesthetic Management and Anesthetic Considerations in a Patient with Situs Inversus Totalis

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Cite this article as: Yılmaz Duran F, Bilgin MU, Direnç Külünk E. Safe Anesthetic Management and Anesthetic Considerations in a Patient with Situs Inversus Totalis. Cyprus J Med Sci 2017; 2: 72-5.

Situs inversus totalis is a rare congenital positional anomaly. We report a successful perioperative management of a 72-year-old-man with situs inversus totalis, coronary arterial disease, and lung cancer scheduled for emergency operation because of ileal perforation under general anesthesia. We recommend that patients with congenital anomalies need to be thoroughly and cautiously evaluated. By this case, we review our anesthetic administration in patients with situs inversus totalis and share our experience with our colleagues.

Keywords: Situs inversus totalis, anesthetic management, safety

INTRODUCTION

Situs inversus (SI) is an uncommon congenital anomaly characterized by a mirror image orientation of the abdominal and thoracic viscera relative to the midline during the embryological development, a 270-degree clockwise rotation instead of normal 270-degree anticlockwise rotation of the developing thoracoabdominal organs, and if it is associated with right-sided heart (dextrocardia), it is called situs inversus totalis (SIT) (1-6). SI was first described by Fabricus, and SIT was first described by Mathew Baillie (1, 4). Incidence of SIT varies from 1:5000 to 1:20000 births (1,5). Except for positional anomaly, cardiac functions are normal (1). Patients with SIT are asymptomatic and have a normal life expectancy (1, 4, 5). It is usually inherited by autosomal recessive, but sometimes it is inherited by X chromosome (4). Radiography, ultrasonography, and computed tomography can be used for diagnosis, but the most preferred method is computed tomography and it is considered as the best diagnostic method for SIT (1, 3, 4). Diagnostic features in plain chest X-ray include dextrocardia, stomach bubble in right side, and liver shadow on left side (3). SI is one of the components of Kartagener's syndrome (primary ciliary dyskinesia), which is a combination of SIT, bronchiectasis, male infertility, and sinusitis (1, 2, 4). We report a case of SIT posted for emergency perforation after we obtained patient's consent from his relatives.

CASE PRESENTATION

A 72-year-old-man with known case of SIT, coronary arterial disease, and lung cancer was presented to emergency operation for ileal perforation. He had been treated by radiotherapy and chemotherapy for lung cancer 5 months ago. He had gastric operation for ulceration 20 years ago. He was under treatment with acetylsalicylic acid and proton pump inhibitor. In the pre-anesthetic evaluation, his Glasgow Coma Scale score was $E_3M_5V_4$. Physical examination revealed consciousness; tend to fall asleep; closed eyes; normal-sized, normally reactive pupils; apex beat was on the right fifth intercostal space in the midclavicular line; heart was auscultated on the right side of the chest; and lung auscultation was evaluated as decreased bilaterally. He had respiratory failure. Abdominal examination revealed tenderness and rigidity in all four quadrants of his abdomen. His pulse rate was 115 beat/min, blood pressure 110/50 mmHg, and body temperature was 36°C. Chest X-ray (Figure 1) and computed tomography (Figure 2) showed dextrocardia with fundal gas shadow on the right side. Electrocardiography (ECG) showed marked right axis deviation (Figure 3); ECG with reverse lead placement showed left axis deviation, Ashman phenomenon, and pathological q-wave in inferior leads (Figure 4); and 2D ECG confirmed dextrocardia with first-degree aortic and tricuspid failure.

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Received: 19.09.2017 **Accepted:** 01.11.2017 **Available Online Date:** 09.01.2018

In the operating room, routine monitoring (electrocardiogram, pulse oximeter, noninvasive blood pressure) was attached and a pre-induction arterial line was placed. The electrocardiogram lead placement was reversed because of the patient's dextrocardia. Anesthesia was induced with pentothal 5 mg/kg, fentanyl 1 µg/kg, and cis-atracurium 0.2 mg/kg uneventfully, and a single lumen endotracheal tube was placed. Anesthesia was maintained with air in O_2 (50%:50%), desflurane (5%-6%); muscle relaxation was maintained with intermittent cis-atracurium boluses. Capnography was also initiated. Because of the history of radiotherapy and chemotherapy, we had difficulty in intravenous cannulation and thus we placed

FIGURE 1. Chest X-ray

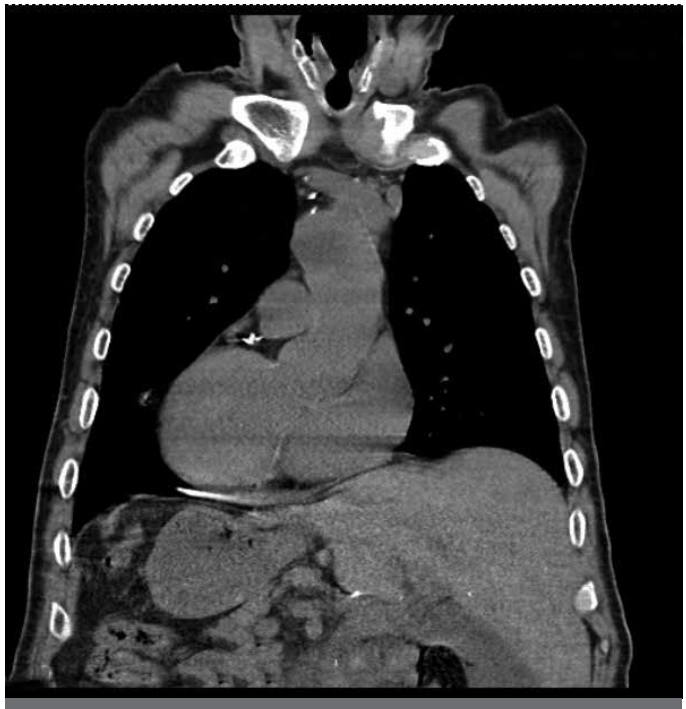

FIGURE 2. Computed tomography of thorax

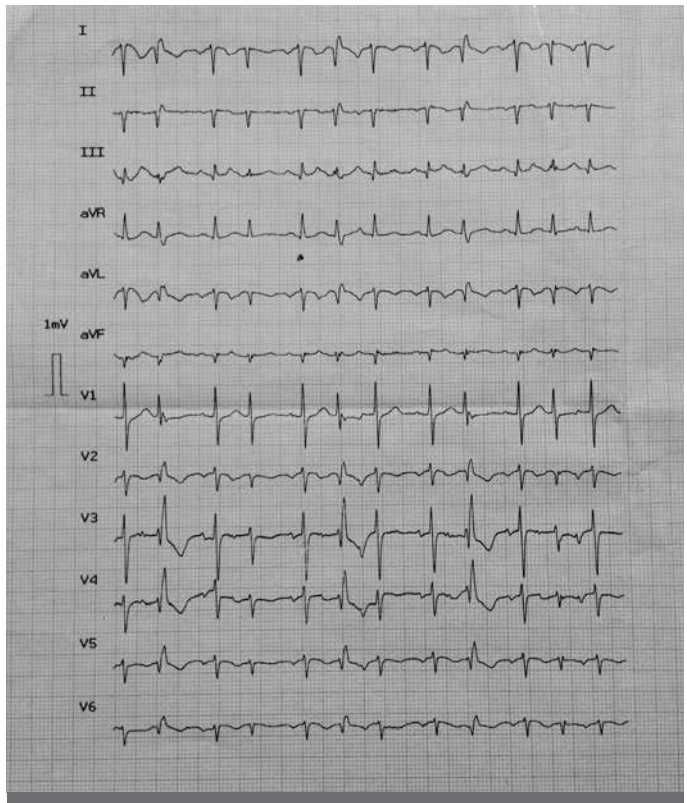

FIGURE 3. ECG (normal lead-placed)
ECG: electrocardiography

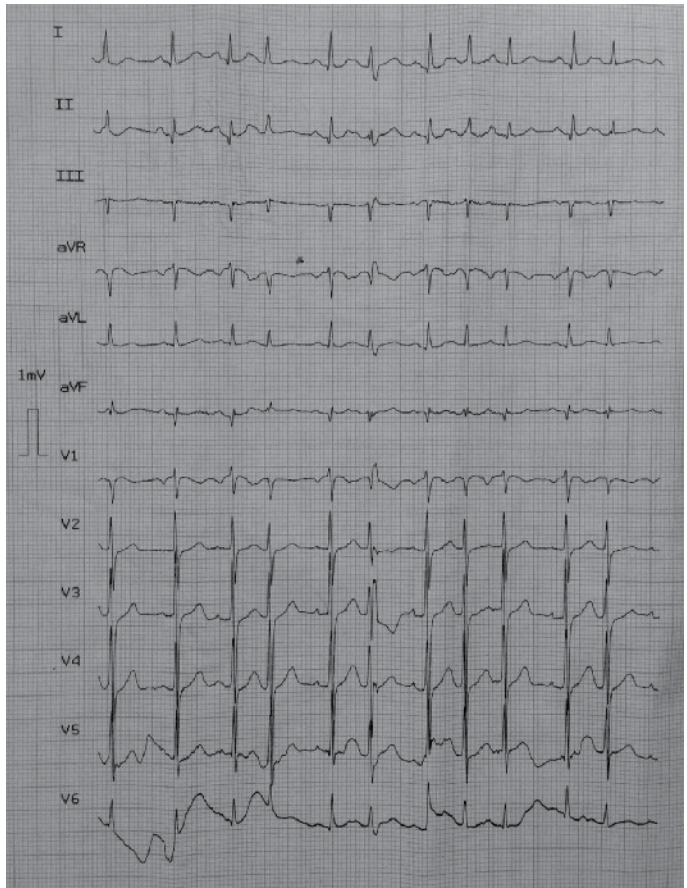

FIGURE 4. Reverse lead-placed ECG (Ashman phenomenon and pathological q-wave in inferior leads)
ECG: electrocardiography

central venous catheter cautiously. He was hemodynamically stable during the perioperative period. At the end of the surgery, he was transferred to the intensive care unit. Postoperative analgesia was maintained with tramadol three times 75 mg intravenously. On the second day of the operation, he was extubated, and he was discharged from the intensive care unit 5 days after the operation.

DISCUSSION

We report a safe anesthetic management of a patient with SIT for emergency ileal perforation. Our patient had diagnostic findings in plain chest X-ray. ECG with reverse lead placement showed no abnormality except arrhythmia.

Situs inversus totalis alone does not cause any significant morbidity. Patients with SIT are asymptomatic and have a normal life expectancy (1, 4, 5). But SIT can coexist with other congenital anomalies, such as cardiovascular, respiratory, digestive system, etc. (6). Also, although SIT is well described by a few medical journals, the anesthetic considerations have not been thoroughly explained. By this case, we want to report precautions in the anesthetic management of the cases with SIT. Precautions that should be taken during the anesthetic management of patients with SIT are:

1. Mainstem intubation can occur on left side of the trachea and should be kept in mind while intubating the trachea (1, 4, 5)
2. If central venous catheter cannulation is planned, preference should be given to left internal jugular vein (to avoid thoracic duct and to ensure direct access to right atrium) (1, 3, 5)
3. All invasive lines such as central venous cannulation, arterial cannulation in major artery, should always be US-guided (3, 5, 6)
4. ECG electrodes and defibrillation pads should be placed in reverse orientation (1-6)
5. Kartagener's syndrome should be considered in these patients (1, 2, 6)
6. Detection and documentation of SI is important to prevent adverse events (1)
7. The intraoperative (6) and postoperative oxygen supplementation should always be humidified especially in cases with Kartagener's syndrome (2, 3)
8. The patient's hydration should be well maintained to prevent any inspissation of secretions in the airway and potential incidence of airway compromise (2)
9. Adequate analgesia should be provided (Inadequate analgesia may lead to respiratory insufficiency in the presence of Kartagener's syndrome) (2)
10. Surgery requires relatively more duration in patients with SIT because tissue handling and orientation were difficult to interpret (2)
11. In prolonged surgery, body temperature should be monitored and normothermia should be actively maintained (2)
12. In thoracic surgery, while choosing a double lumen tube, the anatomy of the bronchi should be considered (6)
13. If Echo/USG is available they may be used briefly to exclude any flaw in a situation of proper Cardio Pulmonary Resuscitation (CPR). Don't hesitate to interrupt, it may save your ineffective CPR time and help in early return of spontaneous circulation (3)
14. Modification in CPR and defibrillation techniques (3, 5, 6)
15. Prolonged paralysis is reported with succinylcholine in SIT (due to decrease in pseudocholinesterase levels) (3, 5, 6)
16. Kartagener's syndrome is associated with airway anomalies, which may cause difficult laryngoscopy and intubation (3, 4, 6)
17. Since it has no effect on thoracic/respiratory muscles and spontaneous respiration, regional anesthesia is a suitable method when indicated (5). But the spinal deformities such as split cord, spina bifida, meningomyelocele, scoliosis, etc., have been described in the literature. When surgery is planned under regional anesthesia, the patient must be evaluated very carefully (10).
18. Pregnant patient maneuvers should be done considering uterus position. It is possible that uterus is relocated on the right side (5).

Prediagnosed SIT patients should be evaluated and examined very carefully. If any sign of SIT is present in any preoperative imaging, examination, or laboratory tests, the diagnosis should be confirmed or excluded. Although there is no distinctive approach for SIT, monitoring should be done accordingly, and any concomitant disease or possible complications should be under consideration.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.Y.D., M.U.B., E.D.K.; Design - F.Y.D., M.U.B., E.D.K.; Supervision - F.Y.D., M.U.B., E.D.K.; Resource - F.Y.D., M.U.B., E.D.K.; Materials - F.Y.D., M.U.B., E.D.K.; Data Collection and/or Processing - F.Y.D., M.U.B., E.D.K.; Analysis and/or Interpretation - F.Y.D., M.U.B., E.D.K.; Literature Search - F.Y.D., M.U.B., E.D.K.; Writing - F.Y.D., M.U.B., E.D.K.; Critical Reviews - F.Y.D., M.U.B., E.D.K.

Acknowledgements: The authors would like to thank Radiology and Cardiology department of the hospital for their assistance.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Case Report

DOI: 10.5152/cjms.2018.284

The Association between Apert Syndrome and Autistic Spectrum Disorder in a Patient of Cypriot Heritage

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Cite this article as: Cengiz Y, Ergören MÇ. The Association between Apert Syndrome and Autistic Spectrum Disorder in a Patient of Cypriot Heritage. Cyprus J Med Sci 2017; 2: 76-8.

Apert syndrome (AS) is the most frequent form of the acrocephalosyndactyly syndromes. It has an estimated incidence of one in 100000 to 160000 newborns.A 3-year-old boy with the karyotype of 46, XY and diagnosed with AS was directed to our clinic for delay in speech acquisition. This is the first case of AS in the Cyprus Island. Due to the mutation in fibroblast growth factor receptor 2 (FGRF2) gene, he was born with the typical phenotype of AS. The Ankara Developmental Screening Inventory (ADSI) was applied to the parents, and the patient was asked some practical directives. The outcome of ADSI showed that the child could be at 13-15 months of developmental age with more than 30% of growth retardation. As per our knowledge, this is the second case of 46, XY child who was diagnosed with acrocephalosyndactyly syndrome and shows a strong association with autistic spectrum disorders.

Keywords: Apert syndrome, autistic spectrum disorder, autism spectrum disorders, Cyprus

INTRODUCTION

The human brain is the outcome of numerous evolutionary processes, and the same mechanism is likely to be involved in the pathogenesis of mental illnesses (1, 2). A negative selection of the risk alleles shows predisposition to mental illnesses, and it is clearly shown in the phenotypes in the society (3). Thus, psychiatric disorders have a strong association with rare and *de novo* mutations (4). However, mostly polygenic predispositions are seen in these disorders (5). Particularly, genetic studies have indicated that common psychiatric disorders are highly polygenic (6, 7). Autism spectrum disorders (ASD) are a group of neurodevelopmental disorders that are generally highly heritable and show significant heterogeneity in genetics, phenotypes, clinical presentation, and associated comorbidities (8). Several common and rare genetic variants are known till date, which have an association with ASD (9). Apert syndrome (AS) is a rare congenital condition with an estimated incidence of 1/100000 to 1/160000 newborns (10). This condition is characterized by craniosynostosis, mid-facial malformations, and complex symmetrical malformations of the hands and feet (11).

Craniofacial deformities, acrocephaly (cone-shaped calvarium), prominent forehead, proptosis, hyperteleorism, and flattened nose with a low bridge are the main clinical manifestations of AS. Oral signs might include pseudocleft, high-arched palate, transverse, and sagittal maxillary hypoplasia, dental crowding, delay in dentition, ectopic teeth, disarrayed teeth, and teeth crowding. Rarely, clinical symptoms related to the central nervous system and the cardiac, gastrointestinal, and urogenital system are noted (12). The mandible is generally normal in size; however, pseudoprognatism can be seen. Several vertebral anomalies have been reported (12, 13).

The mutations within the fibroblast growth factor receptor-2 **(***FGFR2***)** gene on 10q26 locus develop autosomal dominant AS. The *FGFR2* gene encodes the protein responsible for blood vessel formation; wound healing; embryonic evolution; and regulation of cellular division, growth, and maturation with three other FGFRs (13). Additionally, FGFR binds to fibroblast growth factors and plays a significant role in the fusion process of the skull bones (14).

Heterozygosity for 1 of 2 mutation in the exon 7 of the *FGFR2* gene causes AS: S252W and P253R (14, 15). Only two patients had an Alu-element insertion in or near the exon 9 (15). Park et al. (16) reported that there are no statistically significant clinical differences between the 2 major mutations (16). In contrast, Slaney et al. (17) indicated differential effects

This study was presented at the 13th International Conference of Human Genetics, 3-7 April 2016, Kyoto, Japan.

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Received: 12.10.2017
Accepted: 16.12.2017

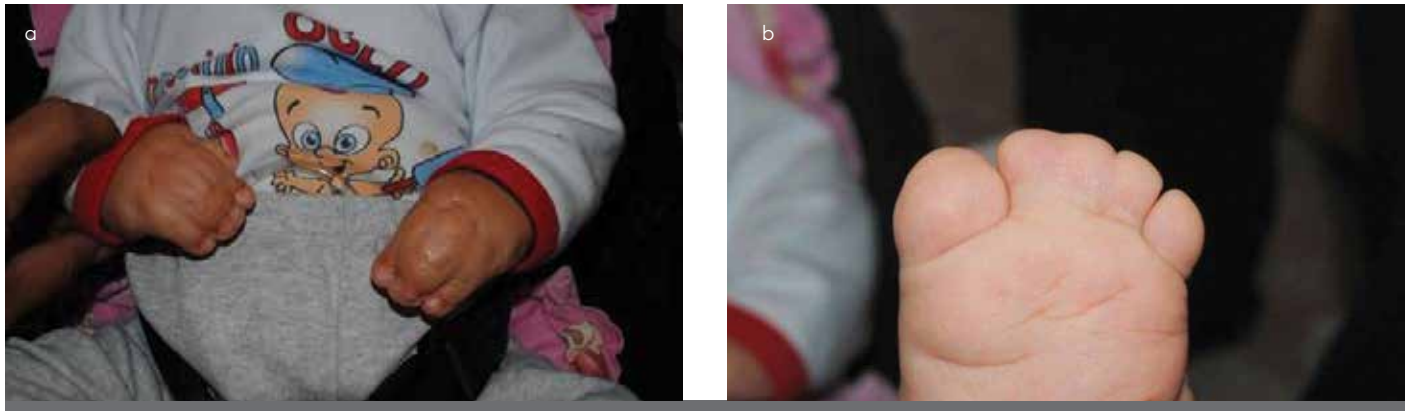

FIGURE I. a, b. (a) Apert type II hand complete syndactyly and partly syndactyly foot before his surgery, (b) apert type II hand partly syndactly foot before his surgery

of the 2 *FGFR2* mutations on syndactyly and cleft palate in AS (17). Syndactyly in both the hands and feet was more severe in patients with the P253R mutation. In contrast, cleft palate was significantly more common in patients with the S252W mutation. No significant differences were found in the prevalence of other malformations associated with AS (17).

Mental retardation is clearly associated with AS in some cases and it is believed that the central nervous system malformations are responsible (18). There are only few articles mentioning a possible association between acrocephalossyndactyly syndromes and developmental delay. In addition, Morey-Cannellas et al. (18) published the first case of a child with AS showing ASD. Herein, we present a 3-year-old boy diagnosed with AS, and we aimed to show a strong association with ASD.

CASE PRESENTATION

A three-year-old boy with the karyotype of 46, XY and diagnosed with AS was directed to our clinic for delay in speech acquisition. This child is the first case of AS in the Cyprus Island.

During clinical assessment, the child was distracted, had increased psychomotor activity, and was avoiding eye contact and social contact; also, he had absence of verbal and non-verbal communication skills and did even use any gestures. He preferred playing alone and could not respond to his name.

The Ankara Developmental Screening Inventory (ADSI), which is the program analyzing the developmental age and mental capability of children aged 0-6 years, was applied to his parents and the child was asked some practical directives (19).

The outcome of ADSI showed that the child could be at 13-15 months of developmental age with more than 30% of growth retardation.

For further analysis, consent forms were provided by the parents, and the medical ethics committee approved the study. A heterozygote P253R mutation within the *FGRF2* gene has been detected by a molecular genetic test. The patient was born with the typical phenotype of AS patients, such as craniosynostosis and type II syndactyly (Figure I, b), bulging and wide-set eyes, and tongue thrust (anterior open-bite) and an underdeveloped upper jaw, mid-facial growth deficiency, and class III malocclusion. Before presenting to our clinic, he had five different surgeries in Turkey and Cyprus at the several hospitals to normalize his life and for survival.

DISCUSSION

As far as we present the case of a child who was diagnosed with acrocephalosyndactyly syndromes and show strong association with ASDs. Since 2003, there has been no case reported with AS and showing ASD.

Autism is an example of a disorder that is more difficult to diagnose, as it is an abnormal behavioral pattern (20). The diagnosis of ASD requires a comprehensive assessment, including (i) a detailed developmental history, (ii) clinical observation/assessment, and (iii) obtaining wider contextual and functional information (20). The symptoms should also be assessed using scales, such as Autism behavior Checklist and Childhood autism rating scale (11).

The patient had to undergo five important surgeries at the early ages of life for normalizing his life and for survival. Therefore, he had long periods of hospitalization and, however his social ambience could be affected. This may lead to psychological problems of development, immature social interactions, isolation, and ostracism.

To date, the knowledge of association between ASD and acrocephalosyndactyly syndromes are still limited with only few examples (18).

CONCLUSION

We presented this case report with the aim that it will raise awareness of a possible association between acrocephalosyndactyly syndromes and ASDs. In the future, research should be conducted to screen a sample of acrocephalosyndactyly cases for ASDs for clarifying whether there is an association. If proven positive, then, a further study of such cases could help clarify the etiology of ASDs.

Informed Consent: Written informed consent was obtained from parents of the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - Y.C., M.Ç.E.; Design - Y.C., M.Ç.E.; Supervision - Y.C., M.Ç.E.; Resource - Y.C., M.Ç.E.; Materials - Y.C., M.Ç.E.; Data Collection and/or Processing - Y.C., M.Ç.E.; Analysis and/or Interpretation

- Y.C., M.Ç.E.; Literature Search - Y.C., M.Ç.E.; Writing - Y.C., M.Ç.E.; Critical Reviews - Y.C., M.Ç.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support..

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Case Report

DOI: 10.5152/cjms.2018.292

Early-Term Perforation after Mitral Valve Repair And Significance of Three-Dimensional Echocardiography

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Cite this article as: Erkal Z, Bayar N, Üreyen ÇM, Arslan Ş. Early-Term Perforation after Mitral Valve Repair And Significance of Three-Dimensional Echocardiography. Cyprus J Med Sci 2017; 2: 79-80.

Diagnosis of complications following valvular surgery is established by echocardiographic examination, principally with transesophageal echocardiography and three-dimensional (3D) echocardiography. Valvular perforation is very rarely seen and is particularly related to infective endocarditis. We present the case of a patient with valvular perforation that occurred in the early postoperative period and was diagnosed using 3D echocardiography.

Keywords: Surgery, perforation, echocardiography

INTRODUCTION

There are early- and late-term complications following valvular surgery. Valvular perforation is very rarely seen and is particularly related to infective endocarditis; it may occasionally be related to iatrogenic causes. Diagnosis is established using echocardiographic examination, principally with transesophageal echocardiography (TEE) and three-dimensional (3D) echocardiography.

CASE PRESENTATION

A 60-year-old male patient who underwent mitral valve repair 2 months ago was admitted to the internal medicine ward for the investigation of the etiology of hemolytic anemia. The patient's physical examination and electrocardiogram results were unremarkable. Transthoracic echocardiography (TTE) and 2D-3D TEE were performed, and severe mitral regurgitation was detected; his blood pressure was 124/68 mmHg. Severe mitral regurgitation was caused by the dehiscence of the mitral ring and perforation of the mitral valve concomitantly (Figure 1, 2). The patient did not have high fever in the 2 months postoperatively, and his white blood count, sedimentation rate, and C-reactive protein level were in a normal range. Reoperation was recommended, and no complications developed after reoperation. We report this case because mitral valve perforation is a very rare complication in the early postoperative period without the presence of infective endocarditis and to emphasize the significance of 3D echocardiography. The patient was confirmed. Informed consent was taken from the patient.

DISCUSSION

Echocardiographic examination is very important in the follow-up of patients who undergo valvular surgery, particularly when a new murmur is noted. Diagnosis of valvular perforation should be kept in mind in the differential diagnosis of eccentric valvular regurgitation (1).

It is difficult to distinguish whether regurgitation is due to valvular perforation. Structural valvular degeneration should be excluded using TEE and particularly 3D echocardiography when hemolysis or a new murmur develops after valvular surgery (2).

Transesophageal echocardiography is an excellent diagnostic modality to reveal detailed anatomic localization of perforation as it provides exact details of mitral valve anatomy because of perfect visualization. Perforation could be confused with chordal rupture, vegetation, or mass; therefore, TEE and particularly 3D echocardiography is very effective in the differential diagnosis (3).

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Received: 28.07.2017
Accepted: 25.12.2017

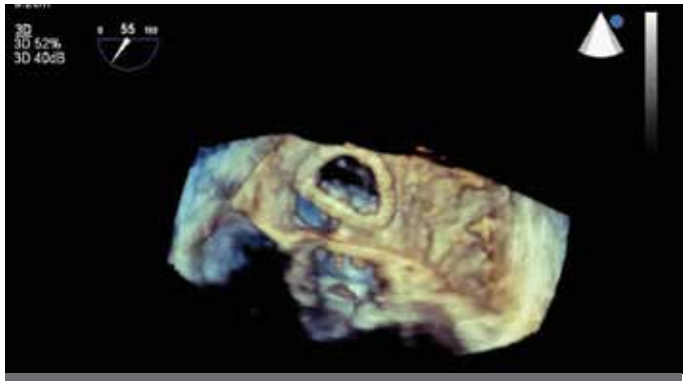

FIGURE I. Two-dimensional transesophageal view of mitral valve perforation

FIGURE 2. 3D transesophageal view of mitral valve perforation

CONCLUSION

Valvular perforation should be kept in mind as a rare complication after valvular surgery. 3D echocardiography should be performed for diagnosis when feasible.

Informed Consent: Written informed consent was ontained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Z.E.; Design - Z.E., N.B.; Supervision - N.B., Ş.A.; Resource - Ç.Ü.; Materials - Z.E., Ç.Ü.; Data Collection and/or Processing - Z.E., N.B.; Analysis and/or Interpretation - Ş.A; Literature Search - N.B.Ç.Ü.; Critical Reviews - Z.E., Ş.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial suport.

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CYPRUS JOURNAL OF MEDICAL SCIENCES

Case Report

DOI: 10.5152/cjms.2018.301

Case Report of Systemic Tularemia in Cyprus

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Cite this article as: Uncu M, Süer K, Kocaoğlu M, Şafak MA, Çağlar K. Case Report of Systemic Tularemia in Cyprus. Cyprus J Med Sci 2017; 2: 81-4.

Tularemia is a zoonotic infectious disease in the Northern Hemisphere, which is caused by gram-negative *Francisella tularensis* bacteria with four subtypes. In this article, a case of a 5-year-old girl with oculoglandular, oropharyngeal, and typhoid tularemia accompanied by lymph nodes in the abdomen has been presented. Amoxicillin–clavulanic acid treatment was first applied to the patient who had high fever, neck lymphadenopathy, and crypts in the tonsils.Intramuscular ceftriaxone therapy was started after the expected response could not be obtained. As a result, as there was no improvement in response to both the treatments in the clinical condition of the patient, and the patient was hospitalized. Physical examination revealed the presence of cervical and submandibular lymphadenopathy and left otitis media. Hepatosplenomegaly and bilateral periorbital edema developed on the day after admission to the hospital. The most frequent diseases in the age group of the patient that may cause the observed findings were tried to be excluded by laboratory and radiological data.Upon learning that the patient had contact with the suspected infected rabbit during treatment, *Francisella tularensis* antibody was ordered for differential diagnosis of tularemia. The test result was reported as 1:80 titre positive. The patient's treatment was changed to a combination of ciprofloxacin plus amikacin. A gradual improvement was observed, and a follow-up evaluation two weeks later revealed that the patient had recovered with no complication. This case is the first proven case feature and is worthy of showing the importance of getting detailed anamnesis.

Keywords: Tularemia, *francisella tularensis*, lymphadenopathy

INTRODUCTION

Tularemia caused by *Francisella tularensis* is transmitted by a direct contact of animals with humans through vectors, infectious aerosols, food, or water.The incubation period is 3–5 days on an average, which can last up to 21 days (1). The disease can be observed in different clinical manifestations according to the bacteria's virulence,entering area, and immune status of the person (2). There are six clinical forms of the disease: ulceroglandular, gastrointestinal, oculoglandular, oropharyngeal, typhoid, and pneumonic form. Patients may present general symptoms, such as fever and pain, and regional lymphadenopathies are often associated with the disease (3). Those living in rural areas, hunters, and veterinarians are considered as risk groups (4). In the Northern Hemisphere, where the disease is more common, ulceroglandular form caused by vectors such as ticks is seen at a high frequency. Oropharyngeal tularemia is the most common form of the disease is observed in Turkey. The agent is often contaminated with contaminated food and water. (1). It is the first case of tularemia reported in the Turkish Republic of Northern Cyprus (TRNC), where fever, pharyngitis, bilateral periorbital edema and hyperemia, mesenteric and cervical lymphadenopathy (LAP), hepatosplenomegaly and diarrhea are observed.

CASE PRESENTATION

A 5-year-old girl who lives in Nicosia city center was admitted to the emergency department with edema, erythema, endurance on the bilateral side, bilateral cervical and submandibular LAPs, fever up to 39°C, and crypt findings in the anterior tonsillar plaque (Figure 1). Amoxicillin-clavulanic acid treatment was started empirically on the patient who had pre-

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Received: 18.11.2017
Accepted: 28.12.2017

viously applied to an external center 7 days ago. The patient's treatment was modified to be intravenous ceftriaxone after growth in the cervical lymph nodes and development of a deep neck infection table..Patient whose condition worsened despite treatment with ceftriaxone was referred to our hospital. During the examination of the patient in emergency department, left otitis media was detected in addition to epicrisis report. .It was reported that LAPs in the jugulodigastric chain on both sides not exceeding 18 mm were observed using neck ultrasonography (USG). Lesions were interpreted as reactive LAP. Abdominal USG revealed LAP in the vicinity of the pancreas. Biochemical parameters except amylase (324 U/L), C-reactive protein (11.13 mg/dL), antistreptolysin O (204 IU/mL), and sedimentation (38 mm/h) levels were within the reference value range. Leukocyte (12880/μL), neutrophil (65%), lymphocyte (25%), monocyte (6%), eosinophil (3%), and basophil (1%) concentrations were reported in the complete blood count and peripheral smear. The postero-anterior chest X-ray results, complete urine analysis, and throat culture studies were normal. The detection of BO 1:320 titer positivity in the Salmonella group agglutination test suggests that there may be a Salmonella infection. Metronidazole was also added to the treatment because of watery, mucous defecation and leukocyte infiltration observed on the stool microscopic examination. On the fourth day of antibiotic treatment, despite regression in fever, in the clinical findings, subclinical LAP enlargement and bilateral periorbital edema and hyperemia were observed (Figure 2). On the patient's control; increased leukocyte count (20,000/μL), LAP of the size 36x23 mm^2 in the pancreas neighborhood and hepatosplenomegaly was observed (Figure 3).There was no growth in blood culture and Salmonella-Shigella media. Suspicion of malignancy was ruled out by the absence of free fluid and pathologic findings in abdominal and thoracic tomography. Serological tests for Epstein Barr IgM profile, Bartonella henselae, cytomegalovirus, toxoplasma, and Wright and Weil–Felix tests were negative. The PPD measurement was 0 mm (no BCG vaccine). After the subfebrile fever began to rise again, ceftriaxone and metranidazole were stopped and the treatment was continued with meropenem. On the sixth day of the meropenem treatment, leukocyte count (13000/μL) and bilateral periorbital edema decreased in the patient whose general condition was good and fever was under control. The next day, there was again an increase in bilateral periorbital edema and hyperemia. The general condition was gradually deteriorated and an increase in the size of the lymph nodes in the cervical and abdominal regions was observed. The fever again became resistant, and diarrhea was re-added to the disease table. In view of the clinical deterioration, it was learned that the patient was contacted with a wild rabbit hunted by his father during the re-questioning of the family. Despite the fact

FIGURE 1. Bilateral periorbital edema and induration

FIGURE 2. Bilateral submandibular lymphadenopathy

FIGURE 3. Mesenteric lymphadenopathy observed in abdominal ultrasonography

that tularemia has not been reported in Cyprus until this day, it has been thought that the patient may also have tularemia. For this purpose, asample for *F. tularensis* micro-agglutination test, which is not performed in our country, was sent to a reference laboratory in the United States of America. Upon learning that the test would be reported in two weeks, the treatment was changed to ciprofloxacin plus amikacin. On the second day of the treatment, bilateral periorbital edema and hyperemia were reduced and cervical LAPs were stretched to1-1.5 cm in size. On the fourth day of the treatment, fever, bilateral periorbital edema, and hyperemia were not observed, and clinical healing was seen. The treatment was continued for 10 days and the patient was later discharged. Meanwhile, the result of the ***F. tularensis*** antibody test was reported as 1:80 titer positive. On the fourteenth day of the treatment, the patient came for the control examination. There were no pathological findings. In cervical and abdominal USG examinations, no LAP and hepatosplenomegaly were observed. Informed consent was obtained from the patient's parents.

DISCUSSION

Tularemia showsdifferent symptoms depending on the agent's entry location and the host's immune system (4).

People who are living in endemic regions and dealing with hunting and other natural sports who are showing the symptoms such as fever, pharyngitis, and LAP, should be detailed questioned in terms of tularemia (1). Since 2005, tularemia has been declared a mandatory disease by the Ministry of Health of the Republic of Turkey. The incidence of tularemia cases has been increasing in Turkey since 2009. The majority of cases are seasonally distributed between December and March (2). The majority of cases observed in Turkey are oropharyngeal tularemia cases (1). In the literature, it has been reported that preauricular, submandibular and anterior cervical LAPs are usually accompanied by other findings in tularemia cases (3).

F. tularensis is susceptible to antibiotics such as fluoroquinolones, aminoglycosides, and tetracycline. The treatment protocol should be planned for at least 10 days for fluoroquinolones and aminoglycosides and not less for 15 days for tetracycline and its derivatives (5).

Sarcoidosis, tuberculosis, cat scratch disease, brucellosis, leprosy, and leishmaniasis should be investigated in the differential diagnosis (3, 6). Considering the fact that the patient is 5 years old, these diseases were excluded in the differential diagnosis, mainly because sarcoidosis is usually seen in older ages and lepra has the average incubation period for 5 years (7).The negativity ofthe ***B. henselae*** IgM and IgG by ELISA tests and the Wright serological agglutination tests have excluded the suspicion of cat scratch disease and brucellosis. The incidence of tuberculosis in TRNC is very low, so BCG vaccination is not routinely given. The applied PPD test was 0 mm. Although there are cases of cutaneous leishmaniasis in our country, there is only one case of Kala Azar that has been reported to this day (8). Leishmaniasis was also excluded from the differential diagnosis because of the absence of skin lesions in our patient and the negative appearance of leishmania visceral antibody test. The familial Mediterranean fever, which has a high incidence in the Mediterranean region, has been ruled out since the fibrinogen level is within the reference value range.

Small mammals such as rabbits, mice, squirrels are considered natural reservoirs for *F. tularensis* (2). For this reason, in those who have a contact story with an animal that is suspected of being infected, the possibility of tularemia should be considered in the presence of long-term fever, throat and / or eye infection findings that do not respond to antibiotics.

The duration of antibody response in Tularemia varies between 1 and 21 days (1). The positive 1:80 titer test result is thought to be related with early sample collection time. LAP findings accompanying with diarrhea and throat and eye infection findings in the patient suggested a systemic tularemia infection together with oculoglandular, oropharyngeal, and typhoid forms. The tularemia confirmation test was not repeated because the patient's family did not want to give blood sample again.

CONCLUSION

According to a report published in 2016 by the European Center for Disease Prevention and Control Center, between 2010-2014 it has not detected any cases in Cyprus (9). Our patient is the first case diagnosed and reported in TRNC. For this reason, we believe that it is important to consider tularemia in the differential diagnosis for early detection cases with similar complaints.

Informed Consent: Written informed consent was obtained from patient's parents who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.U., K.C.; Design - M.U.; Supervision - M.U., K.C., K.S.; Resource - K.C., MA.S.; Materials - M.K., M.U., K.S.; Data Collection and/or Processing - M.K., M.U., MA.S.; Analysis and/or Interpretation - M.U., K.C., K.S.; Literature Search - M.U., K.S.; Writing - M.U., K.C., K.S.; Critical Reviews - M.U., K.C., K.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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