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Original Research Articles: Original prospective or retrospective studies of basic or clinical investigations in areas relevant to medicine.

Content:

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- Material and Methods
- Results
- Discussion
- Reference

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ACKNOWLEDGEMENTS: Conflict of interest, financial support, grants, and all other editorial (statistical analysis, language editing) and/or technical assistance if present, must be presented at the end of the text.

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All of the complaints regarding the articles should be stated via e-mail to tmsj@trakya.edu.tr. TMSJ Editorial Board evaluates the complaints with the accordance of COPE Guidelines and draws a conclusion after the decision of Editor-in-Chief and an ethics editor.

EDITORIAL

Dear readers,

I would like to present you our journal's first issue of 2020. In this issue, you will find 8 articles, consisting of 4 original researches, 1 case series, 1 case report, 1 review and 1 letter to the editor.

Chatzisali et al. tried to find whether cannabinoid receptors play a role in antinociception with an animal experiment. Cengiz et al. presented their findings regarding the quality of life of the patients who had open inguinal hernia mesh repair. Aksu et al. made a detailed analysis of thoracolumbar injuries in a university hospital according to AOSpine classification system. Özyiğit et al. evaluated the effects of night shifts on residents by using The Tower of Hanoi test.

Akay et al. presented a case series with myeloid sarcoma, which is a rare disease. Göztepe et al. drawn our attention to a patient with a single coronary artery anomaly. Adnan wrote a review regarding bispecific antibodies as a new therapeutic approach to rheumatoid arthritis. Finally, Syrioti made a contribution by writing a letter to the editor about one of our previously published articles regarding the retrospective analysis of chronic myeloid leukemia patients. I hope, you find the articles in this issue as entrancing and compelling as I have.

As the new year begins, new editors have joined our editorial team: Bengisu Gür from Bezmialem University, Berkin Ersoy from Hamburg University, Ekin Altınbaş from Acıbadem University, Selin Kolsuz from Koç University and Burak Bardakçı, Elif Cengiz, Mert Yücel Ayrık, Oktay Şişman, Sarper Kızılkaya, Sezin Sayın from Trakya University. It is exciting to work with editors from different universities and I am sure that they will work enthusiastically and do their best to support our journal in every possible way.

I also would like to thank every member of our editorial advisory board and editorial board for their great contributions to every issue of our journal.

Hope to meet our dearest readers in the next issue of TMSJ!

Nur Gülce İŞKAN
Editor-in-Chief

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TMSJ
ORIGINAL ARTICLE

CANNABINOID RECEPTORS ARE NOT INVOLVED IN ANTINOCICEPTION INDUCED BY SYSTEMIC DICLOFENAC IN MICE

Beiza Chatzisali[1], Tolga Gaş[1], Hilmi Kılgın[1], Kübra Duvan Aydemir[2], Dilşat Erümit[2], Ruhan Deniz Topuz[2], Ahmet Ulugöl[2]

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ABSTRACT

Aims: It has been long suspected that the cannabinoid system participates in the antinociceptive effects of nonsteroidal anti-inflammatory drugs. We studied the possible effects of cannabinoid receptor antagonism on diclofenac-induced antinociception in the writhing test in mice. ***Methods:*** In our study, male BALB/c mice, weighing 20-30 g, were used. Writhing responses were produced by intraperitoneal injection of 0.6% acetic acid. Different doses of diclofenac (3, 10, 30 mg/kg, i.p.) were tested, then the influence of AM-251 (1 mg/kg, i.p.), a cannabinoid CB1 receptor antagonist and AM-630 (3 mg/kg, i.p.), a cannabinoid CB2 receptor antagonist on the antinociceptive effects of diclofenac was studied. ***Results:*** Diclofenac administration elicited a significant, dose-dependent antinociceptive response; however, neither the cannabinoid CB1 receptor antagonist AM-251 nor the cannabinoid CB2 receptor antagonist AM-630 had any influence on the antinociceptive effect of diclofenac. ***Conclusion:*** Iinhibition of cannabinoid receptors does not contribute to the antinociceptive action of systemic diclofenac. Further studies are needed to explain the antinociceptive mechanism of diclofenac. ***Keywords:*** AM-251, AM-630, antinociception, cannabinoid receptors, diclofenac

INTRODUCTION

Cannabinoids are a group of chemical compounds, which potentially bind to two recognized cannabinoid receptors (CB1 and CB2). They include natural cannabinoids found in synthetic cannabinoids, the cannabis plant and endocannabinoids and constitute a therapeutic alternative for limited indications (1). Dronabinol and nabilone, two synthetic cannabinoids, are approved for chemotherapy-associated emesis; whereas nabilone is also indicated for AIDS-related weight loss (2). In addition, nabiximols (Δ9-tetrahydrocannabinol [THC]+cannabidiol) is a plant extract approved for spasticity associated with multiple sclerosis, neuropathic pain and cancer pain (3). Due to their unwanted central side effects, such as the risk of abuse, development of tolerance and physical dependence, etc., cannabinoids are used in the clinics only in the abovementioned indications as alternative agents. Understanding their entire mechanism of action will hopefully enable their use in the aforementioned conditions and new indications.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most prescribed medications for treating inflammation, mild to moderate pain, and fever. It is clear that NSAIDs exert most of their effects through inhibition of the activity of cyclooxygenase enzymes (COX-1 and/or COX-2). On the other hand, unlike classical NSAIDs, paracetamol and dipyrone exhibit analgesic activity probably via their action on the central nervous system. Recent investigations suggest that cannabinoid receptors and augmentation of endocannabinoid activity play important roles in the antinociceptive effects of both paracetamol and dipyrone (4, 5). Besides paracetamol and dipyrone, all NSAIDs are expected to increase endocannabinoid tonus both by inhibiting endocannabinoid degradation and by increasing their synthesis via COX inhibition (6, 7). Accordingly, it has been proposed that the endocannabinoid system appears to be involved in

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the antinociceptive effect of some NSAIDs, although there are contradictory findings (6-10, 13).

Diclofenac is the most COX2 selective of the classical NSAIDs acting by inhibiting COX enzyme and widely used for relieving inflammation, pain and fever. Chronic treatment with THC decreased the analgesic effect of diclofenac, whereas combinations of diclofenac with the fatty acid amide hydrolase (FAAH, primary degradative enzyme for the principal endocannabinoid anandamide [AEA]) inhibitor URB597 showed synergistic interaction (14, 15). Here, we investigated whether inhibition of cannabinoid receptors play a key role in the systemic antinociceptive effect of diclofenac.

MATERIAL AND METHODS

Animals & ethics

Experiments were carried out on 2 to 3 month old male BALB/c mice weighing 20-30 g (Center of the Laboratory Animals, Trakya University). There were 12 groups and each group consisted of 6 mice. Mice were maintained under controlled light (12/12 h day/night cycles) and temperature (21 ± 2 °C) conditions with food and water ad libitum. Local "Animal Care Ethics Committee" approved this study (Protocol Code: TÜ-HADYEK-2018/32) and all procedures were conducted according to the guidelines of the Ethical Committee of the International Association for the Study of Pain (IASP) (16).

Study design

The acetic acid writhing test was conducted according to the method described elsewhere (17). Writhing responses were produced by intraperitoneal (i.p.) injection of 0.6% acetic acid in a volume of 10 ml/kg. Immediately after acetic acid administration, writhing responses were videotaped and scored for 20 min. After testing different doses of diclofenac (3, 10, 30 mg/kg, i.p.), the influence of the cannabinoid CB1 receptor antagonist AM-251 (1 mg/kg, i.p.) and the cannabinoid CB2 receptor antagonist AM-630 (3 mg/kg, i.p.) on the antinociceptive effects of diclofenac were investigated. Diclofenac was given 30 minutes before acetic acid injection, and cannabinoid receptor antagonists were administered 10 minutes before diclofenac.

Drugs

Acetic acid and AM-630 were purchased from Sigma-Aldrich (St Louis, MO, USA) and AM-251 was obtained from Tocris (UK), while diclofenac was diluted from commercial preparations. Acetic acid and diclofenac were dissolved in physiological saline, whereas AM-251 and AM-630 were given in 1% ethanol, 1% Tween 80, 20% DMSO and 78% saline. Doses and treatment times of each drug were selected from previous researches (18-20).

Statistical analysis

The data were normally distributed. To analyze the antinociceptive effects of diclofenac, the results were evaluated by analysis of variance (ANOVA), followed by Bonferroni post-hoc test. In all statistical analyses, $p < 0.05$ was considered significant. The results were presented as mean ± SEM of six mice per group.

RESULTS

Antinociceptive effect of diclofenac in the writhing test

As it was expected, diclofenac (10, 30, 100 mg/kg) administration exerted a significant, dose-dependent antinociception in the acetic acid writhing test (* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.0001$, compared to vehicle; Figure 1).

Influence of cannabinoid receptor blockade on diclofenac-induced antinociception

Neither AM-251 (1 mg/kg), a cannabinoid CB1 receptor antagonist nor AM-630 (3 mg/kg), a cannabinoid CB2 receptor antagonist at doses neither elicited any effect on their own nor altered the antinociceptive action of diclofenac when compared with each group other than the vehicle groups († $p < 0.001$, ‡ $p < 0.0001$, compared to vehicle; Figures 2, 3).

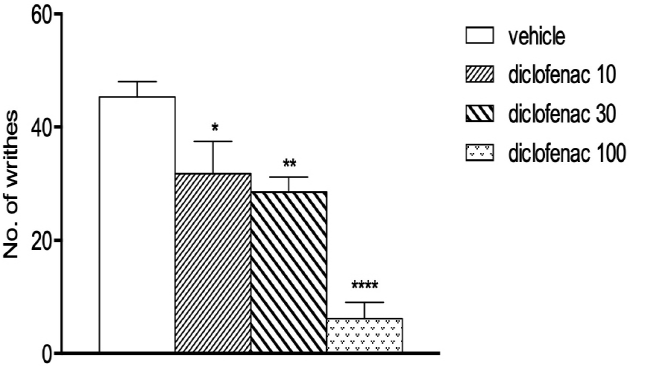

Figure 1: Antinociceptive effect of i.p. injection of diclofenac (10, 30, 100 mg/kg) in the acetic acid writhing test (* p < 0.05, † p < 0.01, ‡ p < 0.0001, compared to vehicle).

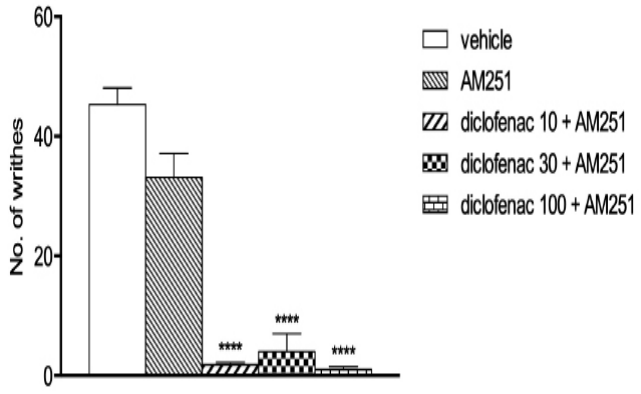

Figure 2: Blockade of antinociceptive effect of systemic administration of diclofenac (10, 30, 100 mg/kg) by the cannabinoid CB1 receptor antagonist AM-251 (1 mg/kg) in the acetic acid writhing test († p < 0.0001, compared to vehicle).

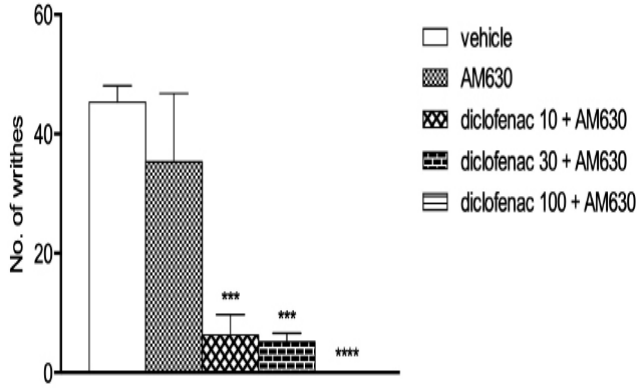

Figure 3: Blockade of antinociceptive effect of systemic administration of diclofenac (10, 30, 100 mg/kg) by the cannabinoid CB2 receptor antagonist AM-630 (3 mg/kg) in the acetic acid writhing test († p < 0.001, ‡ p < 0.0001, compared to vehicle).

DISCUSSION

COX metabolizes arachidonic acid resulting in the synthesis of prostaglandins; there are two isoforms of COX: COX-1 and COX-2 (21). Diclofenac, a classical NSAID, inhibits the enzyme COX and is extensively used for the treatment of mild to moderate inflammation and pain. Here, we investigated whether mechanisms (specifically, cannabinoid receptors) other than COX inhibition play a role in diclofenac antinociception, but our findings indicate that cannabinoid receptors are not involved in the antinociceptive effect of systemic diclofenac.

As we have stated in the introduction, all NSAIDs have the potential of augmenting endocannabinoid levels by inhibiting COX-2 (although with a weak potential) and thereby preventing degradation of endocannabinoids (6, 7, 22). Inhibition of COX enzymes by NSAIDs may also elevate endocannabinoid synthesis due to the availability of arachidonic acid for endocannabinoid synthesis rather than prostaglandin synthesis (6, 7, 22). Moreover, some of the classical NSAIDs have been shown to inhibit FAAH directly and reduce the breakdown of endocannabinoids (9). Finally, inhibition of nitric oxide (NO) by NSAIDs may also attenuate the activation of endocannabinoid transporters and thus augment endocannabinoid levels (6, 22). In addition to its well-known COX inhibitory activity, this final mechanism can be attributed to the antinociceptive effect of diclofenac, since NO-cGMP-K+ channel pathway has been suggested to be involved in the peripheral antinociceptive effect of diclofenac (23).

Two previous research articles were important in leading us to start this project, but our findings were not as we expected. In one of them, co-administration of diclofenac with the FAAH inhibitor URB597 elicited a synergistic antinociceptive effect (15). In the other, THC given chronically decreased efficacy and potency of diclofenac, but this decrease did not appear to be an endogenous cannabinoid release-mediated; moreover, diclofenac was given per os (p.o.) in this study (14).

Cannabinoid receptors have been suggested not to be involved in the peripheral antinociceptive mechanism of diclofenac following intraplantar administration (24). Here, our experiments extend these findings showing that antagonism of cannabinoid receptors does not influence systemic diclofenac administration-induced antinociceptive activity.

Animal Care Ethics Committee Approval: This study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TÜHADYEK-2018/32).

Informed Consent: N/A

Conflict of Interest: The authors declared no conflict of interest.

Author contributions: Concept: RDT, AU. Design: BC, TG, HK, KDA, DE, RDT, AU. Supervision: RDT, AU. Resources: RDT, AU. Materials: BC, TG, HK, KDA, DE, RDT, AU. Data collection and/or processing: BC, TG, HK, KDA, DE, RDT, AU. Analysis and/or Interpretation: BC, TG, HK, KDA, DE, RDT, AU. Literature Search: BC, TG, HK, KDA, DE, RDT, AU. Writing Manuscript: RDT, AU. Critical Review: BC, TG, HK, KDA, DE, RDT, AU.

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REFERENCES

1. Ulugol A. The endocannabinoid system as a potential therapeutic target for pain modulation. Balkan Med J 2014;31:115-20.
2. Schrot RJ, Hubbard JR. Cannabinoids: medical implications. Ann Med 2016;48:128-41.
3. Sastre-Garriga J, Vila C, Clissold S et al. THC and CBD oromucosal spray (Sativex (R)) in the management of spasticity associated with multiple sclerosis. Expert Rev Neurother 2011;11:627-37.
4. Mallet C, Daulhac L, Bonnefont J et al. Endocannabinoid and serotonergic systems are needed for acetaminophen-induced analgesia. Pain 2008;139:190-200.
5. Rogosch T, Sinning C, Podlewski A et al. Novel bioactive metabolites of dipyrone (metamizol). Bioorgan Med Chem 2012;20:101-7.
6. Crunfli F, Vilela FC, Giusti-Paiva A. Cannabinoid CB1 receptors mediate the effects of dipyrone. Clin Exp Pharmacol P 2015;42:246-55.
7. Hamza M, Dionne RA. Mechanisms of non-opioid analgesics beyond cyclooxygenase enzyme inhibition. Curr Mol Pharmacol 2009;2:1-14.
8. Paunescu H, Coman OA, Coman L et al. Cannabinoid system and cyclooxygenases inhibitors. J Med Life 2011;4:11-20.
9. Fowler CJ. NSAIDs: endocannabinoid stimulating anti-inflammatory drugs?. Trends Pharmacol Sci 2012;33:468-73.
10. Elmas P, Ulugol A. Involvement of cannabinoid CB1 receptors in the antinociceptive effect of dipyrone. J Neural Transm 2013;120:1533-8.
11. Schlosburg JE, Radanova L, Di Marzo V et al. Evaluation of the endogenous cannabinoid system in mediating the behavioral effects of dipyrone (metamizol) in mice. Behav Pharmacol 2012;23:722-6.
12. Topuz RD, Gunduz O, Karadag HC et al. Endocannabinoid and N-acylethanolamide levels in rat brain and spinal cord following systemic dipyrone and paracetamol administration. Can J Physiol Pharmacol 2019;8:1-7.
13. Saglam G, Gunduz O, Ulugol A. Blockade of cannabinoid CB1 and CB2 receptors does not prevent the antipruritic effect of systemic paracetamol. Acta Neurol Belg 2014;114:307-9.
14. Anikwue R, Huffman JW, Martin ZL et al. Decrease in efficacy and potency of nonsteroidal anti-inflammatory drugs by chronic delta(9)-tetrahydrocannabinol administration. J Pharmacol Exp Ther 2002;303:340-6.
15. Naidu PS, Booker L, Cravatt BF et al. Synergy between enzyme inhibitors of fatty acid amide hydrolase and cyclooxygenase in visceral nociception. J Pharmacol Exp Ther 2009;329:48-56.
16. Zimmermann M. Ethical guidelines for investigations of experimental pain in conscious animals. Pain 1983;16:109-10.
17. Ulugol A, Ozyigit F, Yesilyurt O et al. The additive antinociceptive interaction between WIN 55,212-2, a cannabinoid agonist, and ketorolac. Anesth Analg 2006;102:443-7.
18. Gencer A, Gunduz O, Ulugol A. Involvement of descending serotonergic and noradrenergic systems and their spinal receptor subtypes in the antinociceptive effect of dipyrone. Drug Res 2015;65:645-9.
19. Yilmaz I, Ulugol A. The effect of nitric oxide synthase inhibitors on the development of analgesic tolerance to dipyrone in mice. Int J Neurosci 2009;119:755-64.
20. Ertin IH, Gunduz O, Ulugol A. Contribution of nociceptin/orphanin FQ receptors to the anti-nociceptive and hypothermic effects of dipyrone. Acta Neuropsychiatr 2015;27:48-52.
21. Vane J, Botting R. Inflammation and the mechanism of action of antiinflammatory drugs. Faseb Journal 1987;1:89-96.
22. Guhring H, Hamza M, Sergejeva M et al. A role for endocannabinoids in indomethacin-induced spinal antinociception. Eur J Pharmacol 2002;454:153-63.
23. Ortiz MI, Granados-Soto V, Castaneda-Hernandez G. The NO-cGMP-K+ channel pathway participates in the antinociceptive effect of diclofenac, but not of indomethacin. Pharmacol Biochem Behav 2003;76:187-95.
24. Silva LCR, Romero TRL, Guzzo LS et al. Participation of cannabinoid receptors in peripheral nociception induced by some NSAIDs. Braz J Med Biol Res 2012;45:1240-3.

TMSJ
ORIGINAL ARTICLE

THE IMPACT OF OPEN INGUINAL HERNIA MESH REPAIR ON QUALITY OF LIFE

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ABSTRACT

Aims: This study aims to evaluate the effect of open inguinal hernia repair with mesh on the quality of life of the patients who were operated at a university hospital. ***Methods:*** In this cohort study, 86 patients who had undergone an open inguinal hernia repair at General Surgery Department in a university hospital between January 2017 and October 2019 were asked to fill out the Carolinas Comfort Scale questionnaire and the data were analyzed retrospectively. ***Results:*** The total number of patients in the study was 86. Seventy-three were male (84%) and 13 were female (16%). The median age was 53 years ranging from 18 to 82. The difference of pre- and post-operative scores revealed high significance in all categories and in total; laying down, bending over, sitting up, performing activities of daily life, coughing or deep breathing, walking or standing, walking up or down the stairs, exercising and total score. ***Conclusion:*** Inguinal hernia decreases the quality of daily life by limiting the movements with groin pain. Surgical low-tension repair with mesh improves the quality of life significantly. ***Keywords:*** Inguinal hernia, quality of life, mesh repair

INTRODUCTION

Inguinal hernia (IH) is the most common of abdominal hernias with a 75% rate according to the National Health Service of the United Kingdom (1). The prevalence of IH is 1.7% in all ages and 4% for people who are aged over 45 (1). About 90% of IH patients are male whereas only 10% are female (2). The main risk factors of IH are family history, age, gender, collagen diseases, and high Body Mass Index (3). Even though there's evidence to suggest that genetics may play a role in having congenital IH, most of the IH cases are acquired (2). Two-thirds of IH patients are symptomatic and the main complaints are protrusion and pain in the groin (3). Generally, the symptoms and a precise physical examination are sufficient for the diagnosis (2).

Several repair techniques for IH are open repair with suture (Shouldice), open repair with mesh (Lichtenstein) and laparoscopic extraperitoneal repair with mesh (TEP) or transabdominal preperitoneal repair with mesh (TAPP) (4). Surgical repair is the most efficient treatment in IH and mesh repair is the gold standard treatment (2, 3). In non-mesh tension repair, sutures put tension on either side of the defect in order to keep it closed thus the tension inhibits the complete healing of the edges (5). Whereas in mesh repair, the mesh acts as a bridge between the sides of the defect thus decreases the tension. With the tension-free nature of the mesh repair, the recurrence rate and the rehabilitation period is reduced compared to non-mesh tension repairs (6).

Quality of life (QoL) after hernia repair is a common point of interest. Both the technical differences and also different meshes are evaluated concerning their impact especially on movement ability and groin pain in different studies. Rutegard et al. (7) found no statistical difference between light or heavyweight polypropylene mesh patients regarding QoL scores. Sanders et al. (8) reported no significant superiority of mesh fixation technologies including fibrin sealants, self-fixing meshes and NB2C glues over conventional suture fixation on postoperative quality of life.

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In the routine practice, 2D polypropylene single layer standard meshes are being used for open inguinal hernia repairs with suture fixation in our state university hospital setting for social security insurance patients.

The aim of this study is to compare the preoperative and postoperative quality of life of the patients who have undergone an open inguinal hernia repair with polypropylene mesh at the General Surgery Department between January 2017 and October 2019.

MATERIAL AND METHODS

This retrospective cohort study was approved by the Scientific Research Ethics Committee of Trakya University Medical Faculty (Protocol Code: TÜTF-BAEK2019/384). 190 patients were included in the study who have undergone an open inguinal hernia surgery at General Surgery Department between January 2017 and October 2019. Only 86 patients who were reached included in this study. Patients were asked to fill out the Carolinas Comfort Scale (CCS) questionnaire by phone call for preoperative and postoperative conditions. The questionnaire consists of 23 questions that measure pain, movement limitations and sensation of the mesh in 8 different categories listed in Table 1. In the preoperative period, the sensation of the hernia sac is questioned instead of the sensation of mesh. Each question carries points on a scale from 0 to 5. At 0 points, no symptoms were seen, while 5 points represented the worst symptoms. The best score (patient with no symptoms) is 0 and the worst score (patient with the worst symptoms) was 115 (9).

The data were analyzed with IBM SPSS version 23.0.0.0. All categories and total scores were analyzed using the Shapiro-Wilk test for normal distribution. Non-normal distribution was observed for each 8 different categories and total score. The Wilcoxon test was used to compare the scores given to each question before and after surgery for all categories and total scores. A p-value of <0.05 was evaluated as statistically significant. Numbers, percentages, median, minimum, maximum variables, 1st quartile and 3rd quartile were used as descriptive statistics for this study.

RESULTS

In this retrospective cohort study, 86 patients who had undergone an open inguinal hernia repair were included after 1-month postoperatively. Not all the patients completed the whole questionnaire, with a sum of 11 patients having some questions missing. However, we conducted the study on a parameter basis of total of 8 parameters. Patients who had given missing data were not included in total score, but they were included in the parameters that they participated in questionnaires (Table 2). Seventy-three (84.9%) patients were male and thirteen (15.1%) were female. All patients' median age was 53 years. The minimum patient age was 18 years and the maximum was 82 years. There was a statistically significant difference between preoperative and postoperative scores of each category (laying down, bending over, sitting up, performing activities of daily living, coughing or deep breathing, walking or standing, walking up or down the stairs, exercising) and the total score ($p<0.001$) (Table 2). The descriptive statistics (median, minimum, maximum variables, 1st quartile and 3rd quartile) are presented in Table 2.

DISCUSSION

In this study, the change in quality of life of the patients who had undergone an open inguinal hernia repair with polypropylene mesh at the General Surgery Department between January 2017 and October 2019, is analyzed. Inguinal hernias are one of the most common afflictions of adults, especially for men (10). Its age and sex distributions are one of the most important epidemiological bases (11). Burcharth et al. (12) found in their study, 88.6% of the patients who had undergone an IH operation are male and 11.4% are female. In our study, there were 73 (84.9%) male and 13 (15.1%) female patients. Similarly, Primatesta et al. (11) reported 27924 inguinal hernia repairs with 91% male dominance. In both studies, it has been shown that inguinal hernia repair prevalence is higher for males than females in all age groups. Moreover, the lifetime risk of developing an inguinal hernia was found 27% for men and 3% for women by Öberg et al. (13). Therefore, a gender-dependent change in the prevalence of inguinal hernia can be stated. The natural pathway of testes from intraabdominal origin to scrotal location, forms a natural anatomical weakness of inguinal region in males. This might be a triggering factor for men having a higher incidence of inguinal hernia. Regarding the relation between age and inguinal hernia, it has been found that the inguinal re-

Table1: Carolinas Comfort Scale questionnaire (7).

Question	Score
While laying down, do you have	
Sensation of mesh	0 1 2 3 4 5
Pain	0 1 2 3 4 5
While bending over, do you have	
Sensation of mesh	0 1 2 3 4 5
Pain	0 1 2 3 4 5
Movement limitations	0 1 2 3 4 5
While sitting up, do you have	
Sensation of mesh	0 1 2 3 4 5
Pain	0 1 2 3 4 5
Movement limitations	0 1 2 3 4 5
While performing activities of daily living (getting out of bed, bathing, getting dressed), do you have	
Sensation of mesh	0 1 2 3 4 5
Pain	0 1 2 3 4 5
Movement limitations	0 1 2 3 4 5
When coughing or deep breathing, do you have	
Sensation of mesh	0 1 2 3 4 5
Pain	0 1 2 3 4 5
Movement limitations	0 1 2 3 4 5
When walking or standing, do you have	
Sensation of mesh	0 1 2 3 4 5
Pain	0 1 2 3 4 5
Movement limitations	0 1 2 3 4 5
When walking up or down the stairs, do you have	
Sensation of mesh	0 1 2 3 4 5
Pain	0 1 2 3 4 5
Movement limitations	0 1 2 3 4 5
When exercising (other than work-related), do you have	
Sensation of mesh	0 1 2 3 4 5
Pain	0 1 2 3 4 5
Movement limitations	0 1 2 3 4 5

Each question scoring 0 for no symptoms and up to 5 for the worst symptoms.

Table 2: Summary of descriptive statistics and p values of 8 different categories and total score.

	Preoperative Scores		Postoperative Scores		p-value
	Median (1st quartile-3rd quartile)	Minimum-Maximum	Median (1st quartile-3rd quartile)	Minimum-Maximum	
Laying down (n=86)	4 (0-10)	0-10	0 (0-0)	0-10	<0.001
Bending over (n=82)	5 (0-15)	0-15	0 (0-0)	0-15	<0.001
Sitting up (n=86)	2.5 (0-15)	0-15	0 (0-0)	0-15	<0.001
Performing activities of daily living (n=85)	3 (0-15)	0-15	0 (0-2)	0-15	<0.001
Coughing or deep breathing (n=84)	5 (2-15)	0-15	0 (0-0)	0-15	<0.001
Walking or standing (n=84)	3.5 (0-15)	0-15	0 (0-0)	0-15	<0.001
Walking up or down stairs (n=84)	5.5 (0-15)	0-15	0 (0-0)	0-15	<0.001
Exercising (n=80)	4 (0-15)	0-15	0 (0-0)	0-15	<0.001
Total Score (n=75)	38 (2-115)	0-115	0 (0-2)	0-115	<0.001

pair peaks bimodally at early childhood and old age for both sexes (12). Primatesta et al. (9) showed that from 2738 emergency admissions with an operation on inguinal hernia, 573 (21%) were performed on infants and 1133 (41%) on patients ≥ 65 years. They also found that rates for elective surgery had increased up to late middle-age after a peak in infants and decreased slightly at elderly ages (11). However, there are no patients under 18 in our study.

In the current trial, 46 questions asked in total consisting of 23 questions about preoperative and 23 questions about postoperative periods. The questions included 8 main categories such as laying down, bending over, sitting up, performing activities of daily living, coughing or deep breathing, walking or standing, walking up or down the stairs, exercising. A high score meant the worse quality of life and with inguinal hernia repair, the scores decreased drastically in each of the 8 categories and in total score, which correlates with our hypothesis. The p-values were less than 0.001 in each category, which is statistically significant. Knox et al. (14) had a similar result in their study about quality of life after surgery. Their study confirmed that as there's a crucial change in the quality of life after hernia repair, the postoperative scores were significantly less than the preoperative scores (14). Lawrence et al. (15) also conducted a similar study about quality of life after hernia repair with another quality of life scale called Short Form 36. This form is a global measure of health-related quality of life that measures the physical and mental health perception before and after the operation (16). Their results also demonstrate the improvement in quality of life of patients who had undergone inguinal hernia repair. These values are also statistically significant again correlating with our results.

Only 86 out of 190 patients responded to questions, excluding the rest from the study. However, this exclusion did not seem to affect the results of the study due to the high significance of scores. The main limitation was that all of the patients responded to the questionnaires in postoperative periods. However, a cross-sectional analysis may give a broader and more realistic score, especially for preoperative discomfort.

In conclusion, our study showed that inguinal hernia repair with mesh makes a crucial improvement in patients' quality of life regarding different daily activities.

Ethics Committee Approval: This retrospective study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (TUTF-BAEK2019/384.

Informed Consent: Written informed consent was obtained from the participants of this study.

Conflict of Interest: The authors declared no conflict of interest.

Author contributions: Concept: EC, TKA, HSÇ, TD. Supervision: EC, TKA, HSÇ, TD. Resources: EC, TKA, HSÇ, TD. Materials: EC, TKA, HSÇ, TD. Data collection and/or processing: EC, TKA, HSÇ, TD. Analysis and/or Interpretation: EC, TKA, HSÇ, TD. Literature Search: EC, TKA, HSÇ, TD. Writing Manuscript: EC, TKA, HSÇ, TD. Critical Review: EC, TKA, HSÇ, TD.

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REFERENCES

1. Jenkins JT, O'Dwyer PJ. Inguinal hernias. BMJ 2008;336(7638):269–72.

2. Hammoud M, Gerken J. Inguinal hernia. StatPearls (serial online) 2019 Jan (cited 2019 Feb). Available from: URL: https://www.ncbi.nlm.nih.gov/books/NBK513332/?report=reader#_NBK513332_pubdet_.

3. HerniaSurge Group. International guidelines for groin hernia management. Hernia 2018;22(1):1-165.

4. Sharma P, Boyers D, Scott N et al. The clinical effectiveness and cost-effectiveness of open mesh repairs in adults presenting with a clinically diagnosed primary unilateral inguinal hernia who are operated in an elective setting: systematic review and economic evaluation. Health Technol Assess 2015;19(92):1-142.

5. Naguib N, ElSamerraai A. No-mesh inguinal hernia repair with continuous absorbable sutures: is it a step forward or backward?. Saudi J Gastroenterol 2009;15(1):68-9.

6. Bringman S, Ramel S, Heikkinen TJ et al. Tension-free inguinal hernia repair: TEP versus mesh-plug versus Lichtenstein: a prospective randomized controlled trial. Annals of surgery 2003;237(1):142-7.

7. Rutegård M, Gümüşçü R, Stylianidis G et al. Chronic pain, discomfort, quality of life and impact on sex life after open inguinal hernia mesh repair: an expertise-based randomized clinical trial comparing lightweight and heavyweight mesh. Hernia 2018;22(3):411-18.

8. Sanders DL, Waydia S. A systematic review of randomised controled trials assessing mesh fixation in open inguinal hernia repair. Hernia 2014;18:165–176.

9. Heniford BT, Walters AL, Lincourt AE et al. Comparison of generic versus specific quality-of-life scales for mesh hernia repairs. J Am Coll Surg 2008;206(4):638-44.

10. Turaga K, Fitzgibbons RJ, Puri V. Inguinal hernias: should we repair? Surg Clin North Am 2008;88:127–38.

11. Primatesta P, Goldacre MJ. Inguinal hernia repair: incidence of elective and emergency surgery, readmission and mortality. Int J Epidemiol 1996;25:835–9.

12. Burcharth J, Pedersen M, Bisgaard T et al. Nationwide prevalence of groin hernia repair. PLoS One 2013;8(1): e54367.
13. Öberg S, Andresen K, Rosenberg J. Etiology of inguinal hernias: acomprehensive review. Front Surg 2017;4(52):1-8.
14. Knox RD, Berney CR. A preoperative hernia symptom score predicts inguinal hernia anatomy and outcomes after TEP repair. Surg Endosc 2015;29(2):481–6.
15. Lawrence K, McWhinnie D. Quality of life in patients undergoing inguinal hernia repair. Ann R Coll Surg Engl 1997;79(1):40-5.
16. Lins L, Carvalho FM. SF-36 total score as a single measure of health-related quality of life: scoping review. SAGE Open Medicine 2016;4:1-12.

TMSJ
ORIGINAL ARTICLE

EVALUATION OF THORACOLUMBAR INJURIES IN TRAKYA UNIVERSITY SCHOOL OF MEDICINE ACCORDING TO AOSPINE CLASSIFICATION SYSTEM

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ABSTRACT

Aims: This study aims to classify the thoracolumbar spinal injuries that were treated in Trakya University School of Medicine according to the recent Thoracolumbar AOSpine injury score and crosscheck the classified data with categorical modifiers such as gender, trauma type and treatment type. ***Methods:*** AOSpine Classification System was used to classify thoracolumbar spinal injuries. Classes were compared with patients' gender, age, trauma energy and treatment type. Pearson Chi-Squared test and Shapiro-Wilk test were used for statistical analysis. ***Results:*** The total number of patients was 248. One hundred fifty-two (61.3%) were male and 96 (38.7%) were female. One hundred and three (86.6%) patients had high-energy trauma and 16 (13.4%) patients had low-energy trauma in a total of 119 operated patients. Relationship between treatment type and AOSpine Classification System statistically significant. There was also a significant difference between trauma energy and AOSpine Classification System types. ***Conclusion:*** As a conclusion, gender and trauma energy were found to have a relationship and higher energy traumas were most likely to cause spinal fractures. In addition, AOSpine classification system may be one of the confounding factors regarding the choice of treatment. ***Keywords:*** Classification, spine, injury

INTRODUCTION

The most common types of injuries in the spinal cord are thoracolumbar fractures (1). The thoracolumbar segment between T11-L2 is exposed to more stress than other parts of the spine. Therefore, ninety percent of the fractures of the spine are in the thoracolumbar region (2). These injuries are usually caused by motor vehicle accidents or falling from a height. The type and intensity of these fractures depend on the age of the patient, the position of the body at the time of trauma and some other factors. Systematic classification of the thoracolumbar fractures is used for the proper diagnosis and treatment of fractures (1). Holdsworth introduced the Two-Column Concept and made a significant novelty in the thoracolumbar fracture classification. He divided the spinal cord into the anterior column (consisting of the vertebral body and disc) and the posterior column (consisting of the facet joint and posterior ligamentous complex). Holdsworth classified fractures as anterior wedge compression fracture, dislocation, rotational fracture-dislocation, extension injury, burst fracture, and shearing fracture (3).

Denis described a three-column theory in 1983 (4). According to this definition, the anterior column consists of the anterior longitudinal ligament anterior annulus fibrosus, and the anterior component of the vertebral body. The middle column consists of the posterior longitudinal ligament, the posterior vertebral wall, and the posterior annulus fibrosus. All the structures behind the posterior longitudinal ligament form the posterior column. In Denis classification, fractures are classified as compression fractures, burst fractures, seat-belt fractures, and fracture-dislocations (5).

Thoracolumbar Injury Classification and Severity (TLICS) Scale is often used by clinicians and radiologists to classify thoracolumbar fractures for developing an appropriate therapeutic strategy. For the

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classification of thoracolumbar fractures according to TLICS, 4 parameters are mainly used: morphology, neurological status, spinal cord, conus medullaris injury, and posterior ligamentous complex. Morphology is used to identify the sort of fracture. Other factors are used to diagnose the presence and level of the fracture (1). Vaccaro et al. (6) promulgated the AOSpine thoracolumbar spine injury classification system in 2013, which includes important elements of both the Magerl classification system and the TLICS.

Three main parameters are evaluated the AOSpine thoracolumbar spine injury classification: morphologic classification of the fracture, neurological status, clinical modifiers (7). Fractures are divided into 3 types, according to this classification system: Type A used for compression injuries; type B for tension band injuries and type C for translation injuries. Type A injuries are divided into 5 subgroups, type B injuries are divided into 3 subgroups. Neurological evaluation is classified as N0 for a neurologically intact patient, N1 for the transient neurological deficit, N2 for symptoms of radiculopathy, N3 for incomplete spinal cord injury or cauda equina injury, N4 for complete spinal cord injury and NX is used to identify patients who cannot be examined. Besides, the patient is evaluated for patient-specific circumstances: M1 is used for injuries where the posterior ligamentous complex condition is ambiguous and M2 is used to designate patient-specific comorbidity (7).

Several reliability analyses were made for the AOSpine Classification System for Thoracolumbar Injuries both worldwide by Kepler et al. (8) and regional analyses in countries like China by Cheng et al. (9) and Iran by Azimi et al. (10) throughout the years. Abedi et al. (11) published a systematic review of reliability and validity for this classification including all the valid reliability analyses published until 2019. Additionally, a revision proposal for this classification was presented by Reinhold et al. (12). Further studies are expected to make this classification accepted and frequently used worldwide.

Our study aims to classify the thoracolumbar spinal injuries that were treated in Trakya University School of Medicine according to the recent Thoracolumbar (TL) AOSIS and to crosscheck the classified data with categorical modifiers such as gender, trauma type and treatment type to see whether there is any relation present.

MATERIAL AND METHODS

This retrospective study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TÜTF-BAEK 2019/355). In this retrospective study, the data of all patients who had admitted to Trakya University School of Medicine Orthopedics and Traumatology Department with thoracic and lumbar spine injury between January 1st, 2009 and June 1st, 2019 were collected and analyzed. Patients who rejected the treatment, patients with wrong diagnoses and patients with missing data were excluded from the study.

Gender, trauma or consultation date, trauma type - if any (high or low energy)-, trauma location (thoracic or lumbar vertebrae) and treatment type (operative or non-operative) of the patients were collected from the archives of Trakya University School of Medicine. MRI, X-Ray and CT files of the patients were used to classify the spinal injuries according to TL AOSIS (Figure 1). Only morphologic statuses were used to classify the injuries.

The data were analyzed using TURCOSA statistical software. A p-value <0.05 was set for the statistical significance. Shapiro-Wilk test and Kolmogorov-Smirnov test was used to test the normality of variables. Pearson Chi-Squared Test ($\chi 2$) was conducted on categorical variables (gender, trauma type, trauma location, and treatment type). Mann Whitney U test was used for non-parametric variables whereas the T-test was used for parametric variables. Numbers and percentages were used as descriptive statistics. The data were compared as gender-trauma energy, gender-treatment, and treatment-injury location. Additionally, AOSpine classification groups were compared with trauma energy, injury location and treatment procedure. Normally distributed variables were given as mean ± standard deviation whereas non-normally distributed variables were given as median (interquartile range).

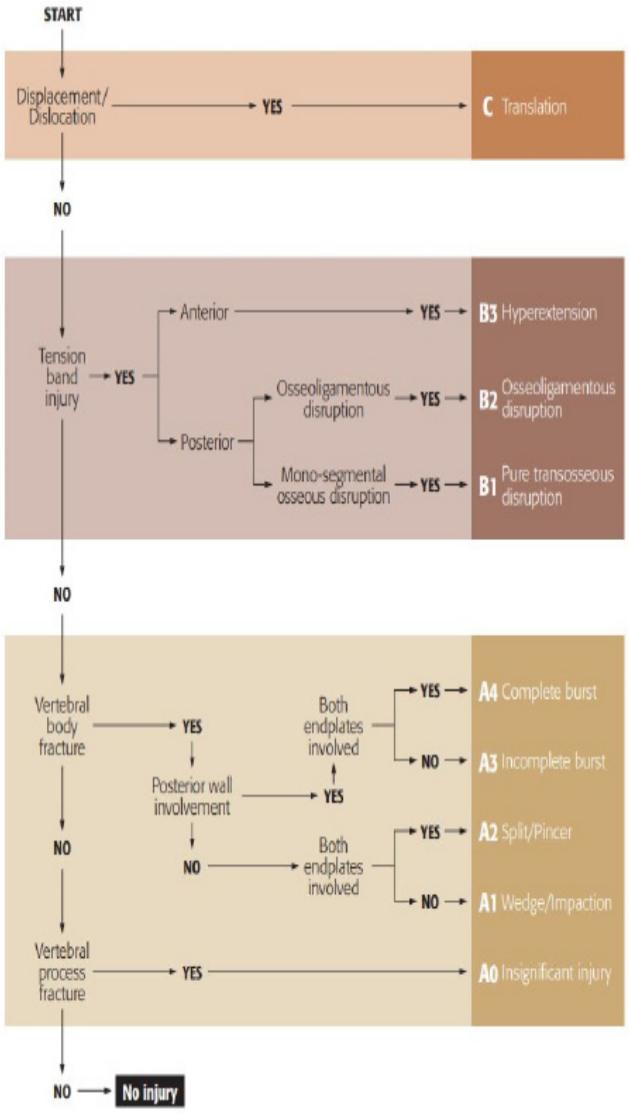

Figure 1: AOSpine thoracolumbar classification system.

RESULTS

In this retrospective study, 218 patients were included. One hundred and thirty three (61%) of them were male and 85 (39%) of them were female. Sixty-five (61.32%) of the male patients were treated surgically and 68 (60.71%) were treated conservatively; 41 (38.68%) of the female patients were treated surgically and 44 (39.29%) were treated conservatively. There was no statistically significant relationship between gender and treatment (p=0.927). When male and female patients were compared in terms of trauma energy, a statistical significance was found (p<0.001) (Table 1).

A0 (21.8%) and A3 (22.6%) type fractures were frequently seen in male patients, while A3 (35.3%) and A4 (23.5%) type fractures were frequently seen in female patients, but this was not statistically significant (p=0.071) (Table 2). In addition, a statistical significance was not found between gender and the number of fractures which is shown in Table 3 (p=0.513). Table 4 shows the relationship between the injury location and trauma energy which has no statistical significance (p=0.117).

Two hundred eighteen patients were classified with the AOSpine Classification System according to the injury location. Fifty-two (73.24%) of the thoracic injuries were subtype A, 18 (25.35%) were subtype B and 1 (1.41%) was subtype C. One hundred and sixteen (92.8%) of lumbar injuries were subtype A, 8 (6.4%) were subtype B and 1 (0.8%) was subtype C. Both thoracic and lumbar injuries were all subtype A. There was a significant relationship between fracture types and injury location (p<0.001).

The mean age of 218 patients was 51.28 years. The mean age of 71 patients with thoracic injury was 50.1 years, the mean age of 125 patients with lumbar injury was 51.6 years and the mean age of 22 patients with thoracal and lumbar injury was 53 years. However, there is no statistically significant relationship between age and injury site (p=0.776). There is a statistically significant difference between AO categories and terms of terms of mean age (p<0.001) (Table 5) as well as between trauma energy and mean age. The age distribution of low energy injuries was higher than the age distribution of high energy injuries (p<0.001) (Table 6). The relation between AOSpine Classification System and treatment was shown in Table 7 and the relation between AOSpine Classification System and the number of fractures was shown in Table 8. Additionally, when trauma energy and AOSpine Classification groups are compared, a statistically significance was found (p=0.018) (Table 9).

Table 1: The relation between gender and trauma energy.

		Gender				
		Male n (%)	Female n (%)	Total n	P Value	Pearson Chi-square value
Trauma Energy	High	122 (67.03%)	60 (32.97%)	182	<0.001	15.6847
	Low	11 (31.43%)	24 (68.57%)	35		
	Total	133	84	217		

Table 2: The relation between AOSpine classification and gender.

		AOSpine Classification											
		A0	A1	A2	A3	A4	B1	B2	B3	C	Total	P Value	Pearson Chi-square value
Gender	Male n (%)	29 (21.8%)	27 (20.3%)	8 (6%)	30 (22.6%)	21 (15.8%)	7 (5.3%)	7 (5.3%)	2 (1.5%)	2 (1.5%)	133	0.071	14.4376
	Female n (%)	15 (17.6%)	5 (5.9%)	5 (5.9%)	30 (35.3%)	20 (23.5%)	3 (3.5%)	6 (7.1%)	1	0 (1.2%)	85 (0%)		
	Total n	44	32	13	60	41	10	13	3	2	218		

Table 3: The relation between number of fracture and gender.

		Number of Fracture			
		Single	Multiple	Total	P Value
Gender	Male n (%)	77(57.89%)	56(42.11%)	133	0.513
	Female n (%)	53(62.35%)	32(37.65%)	85	
	Total n (%)	130	88	218	

Table 4: The relation between injury location and trauma energy.

		Injury Location					
		Thoracic n (%)	Lumber n (%)	Thoracic + Lumber n (%)	Total n	P Value	Pearson Chi-square value
Trauma Energy	High	62(34.07%)	99(54.4%)	21(11.54%)	182		
	Low	9(25.71%)	25(71.43%)	1(2.857%)	35		4.2983
	Total	71	124	22	217	0.117	

Table 5: The relation between AOSpine classification system and age.

		AOSpine Classification									
		A0	A1	A2	A3	A4	B1	B2	B3	C	P Value
Age (years)	n	44 (20.1%)	32 (14.6%)	13 (6%)	60 (27.5%)	41 (19%)	10 (4.5%)	13 (6%)	3 (1.3%)	2 (1%)	
	Median	43.5	40.5	68.0	54.5	60.0	45.5	51.0	61.0	62.5	
	1st quartile	32	28.75	54	38.75	46	36	35	40.5	51.75	0.001
	3rd quartile	56.25	59.25	77	61.5	71	56.5	61	65.5	73.25	

Table 6: The relation between trauma energy and age.

		Age				
		N	Median	1st quartile	3rd quartile	P Value
Trauma Energy	High	182	48.5	16	90	<0.001
	Low	35	71	11	94	
	Total	217				

Table 7: The relation between AOSpine Classification System and treatment.

		AOSpine Classification				
		A	B	C	Total	P Value
Treatment	Operative n (%)	81 (76.4%)	23 (21.7%)	2 (1.9%)	106	<0.001
	Non-operative n (%)	109 (97.32%)	3 (2.68%)	0 (0%)	112	
	Total n	190	26	2	218	

Table 8: The relation between AOSpine classification system and number of fracture.

		AOSpine Classification									
		A0	A1	A2	A3	A4	B1	B2	B3	C	P Value
Number of Fracture	Single	7 (5.38%)	16 (12.31%)	8 (6.15%)	43 (33.08%)	37 (28.46%)	7 (5.38%)	10 (7.69%)	1 (0.77%)	1 (0.77%)	<0.001
	Multiple	37 (42.05%)	16 (18.18%)	5 (5.68%)	17 (19.32%)	4 (4.55%)	3 (3.41%)	3 (3.41%)	2 (2.27%)	1 (1.14%)	
	Total	44	32	13	60	41	10	13	3	2	

Table 9: The relation between AOSpine classification system and trauma energy.

		AOSpine Classification									
		A0	A1	A2	A3	A4	B1	B2	B3	C	P Value
Trauma Energy	Low	2 (5.71%)	5 (14.29%)	6 (17.14%)	13 (37.14%)	8 (22.86%)	0 (0%)	1 (2.86%)	0 (0%)	0 (0%)	0.018
	High	42 (23.08%)	27 (14.84%)	7 (3.85%)	46 (25.27%)	33 (18.13%)	10 (5.49%)	12 (6.59%)	3 (1.65%)	2 (1.1%)	
	Total	44	32	13	59	41	10	13	3	2	

DISCUSSION

In this study, the thoracolumbar spine injuries treated in Trakya University School of Medicine were classified according to the most recent thoracolumbar injury classification system TL AOSIS. The frequency of the injury types were analyzed and the classified injuries were crosschecked with the other variables (treatment procedure, gender, age, trauma type, injury location). Only morphological statuses of the injuries were included in the classification as a result of lacking information about neurological statuses and clinical modifiers of the patients.

Among the 217 patients with thoracolumbar injuries, 61.3% were male and 38.7% were female; the male-to-female ratio was 1.58 to 1. This ratio stays approximately the same when the non-operated and operated patients were categorized according to their genders. However, this finding was not statistically significant. The male predominance was similiar with the literature (13-15). The difference between the treatment methods and gender was also statistically insignificant as well as the study of Dodwad SN et al. (13). In the male population, 8.2% of injuries were caused by low energy trauma. However, in the female population, the percentage of low energy trauma was increased to 28.6% of which 79.1% being over the age of 55 . These findings were similar to the review by Schousboe JT et al. (14) which may be attributed to the fact that osteoporosis being more prevalent in women (16). Patients who were over the age of 55 consist 80% of the 35 patients who were injured as a result of low energy trauma even though the number of patients may not be sufficient to come up with a strong hypothesis, this data might suggest a higher tendency of bone fragility in older women than men.

Most of the thoracolumbar injuries in this study were located in the lumbar region of the spine (57.3%). In another research by Sidon et al. (15), lumbar spinal injuries were found to be the majority in terms of overall spinal fractures supporting our findings. Sidon et al. (15) also state that lumbar fractures were found to be more frequent in women than men and this statement was also supported by another research by Hoy et al. (17). Similar to these researches, lumbar spinal injuries were found to be slightly higher in women (62.6%) than men (60.4%). However the data was insignificant in this study and the 2% difference between genders was not high enough to strongly support the mentioned studies. When classification of subtypes for overall thoracolumbar injuries were compared, A-type injuries were observed to be the most common and C type were the least common fracture type corresponding to the findings of the research by Rajasekaran et al. (18). On the contrary, the most common fracture subtype was A3 in our study which was different than the research by Rajasekaran et al. (18) in which the most common fracture subtype was B2. This could show that a generalization about subtypes' frequency cannot be made although A and C type injuries might be accepted as the most and least common fracture types respectively, considering the mechanism and the severity of the fractures and the statistics of the research by Rajasekaran et al. (18). Further studies are needed in this matter. According to the analyzed data, A-type fractures were more common in the thoracic spine (73.24%). This might lead us to assume a relationship between the localization and the type of fracture.

The relationship between the trauma energy and the treatment was not significant. Operatively and non-operatively treated patients were distributed almost equally in high-energy-related trauma patients different from in low-energy-related trauma patients as most of the group (62.9%) was composed of non-operatively treated patients. The findings were similar for patients older than 55. However, there was a statistical significance found between TL AOSIS subtypes regarding the trauma energy. This significance was noticeable in the A2 subgroup and further as the low-energy-related trauma percentage decreases while the subgroups proceed towards Type C fractures with one exception on the B2 subgroup which may be the cause of the insufficient number of patients for each subgroup in Type B fractures. Another remarkable finding in this retrospective study was the relationship between the AOSpine TLICS subgroups and the treatment. There was a statistically significant relationship between the fracture types and the choice of treatment ($p<0.001$). The data showed that as the fracture types progressed from A subgroups towards C group, the percentage of surgical intervention increased visibly. It is believed that the inconsistency in Type B subgroups was caused by the insufficient number of patients as it is stated previously. The relationships between AOSpine TLICS subgroups and the trauma energy and treatment correlate with the Thoracolumbar AOSpine Injury Score developed by Kepler et al. (19) and a research made to help with the treatment of spinal injuries depending on the subtypes which suggest as the subgroups progress the severity score of the injury and chance of surgical intervention increases (7).

The mean age of the patients was crosschecked with other variables and there was an interesting statistical significance found between the AOSpine TLICS groups

(p<0.001). Type C injuries were excluded in this matter because of the insufficient number of patients. This statistical significance was caused by the mean age differences between A2-A0, A4-A0, A2-A1, A4-A1. Type B groups that had not enough number of examples did not cause any statistical significance. It could be hypothesized that if the number of injuries evaluated increases a connection could be found among the subgroups and mean age of the related patients. Another and relatively important statistical significance observed was between the trauma energy and the mean age of the related patients. While the mean age of the patients who experienced low-energy-related trauma was 71 years, the mean age concerning the high-energy-related trauma was 48.5 years which would show a remarkable difference between high and low-energy-related trauma. Similarly, when the patients older and younger than 55 years were crosschecked with trauma energy; 80% of the low-energy-related trauma was observed in the patient group older than 55 years showing us an important and statistically significant result. Therefore, the increase in severity causes an increase in the surgical intervention need and a tendency towards being the result of high-energy-related traumas. This is probably because of the changes in BMD and general bone structure for both males and females which was mentioned in numerous studies in the literature (15, 20, 21).

There were some significant limitations in the study, the main one being the low number of patients for some of the observation groups like C Group injuries and lack of information about the other modifiers such as neurologic status and patient-specific modifiers in the patients' archive files. Nonetheless, we used most of the available information to minimize the limitations. To see a more accurate distribution of the subtypes and other modifiers and achieve concrete results, larger sample groups were needed.

As a conclusion, gender and trauma energy were found to have a relationship and higher energy traumas were most likely to cause spinal fractures. In addition, the results of our study showed that the AOSpine classification system may be one of the confounding factors regarding the choice of treatment such as conservative or operative. Similarly, age was an effective factor for the changes in general bone structure making older patients vulnerable to serious injuries even as a result of low-energy-related trauma. Further studies are needed to specify the frequency of TL AOSIS subtypes and clarify the effects of fracture types, neurological status and patient-specific modifiers on the treatment.

Ethics Committee Approval: This retrospective study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (TÜTF-BAEK 2019/355)

Informed Consent: Written informed consent was obtained from the participants of this study.

Conflict of Interest: The authors declared no conflict of interest.

Author contributions: Concept: GA, SS, MSO, MÇ. Supervision: GA, SS, MSO, MÇ. Resources: GA, SS, MSO, MÇ. Materials: GA, SS, MSO, MÇ. Data collection and/or processing: GA, SS, MSO, MÇ. Analysis and/or Interpretation: GA, SS, MSO, MÇ. Literature Search: GA, SS, MSO, MÇ. Writing Manuscript: GA, SS, MSO, MÇ. Critical Review: GA, SS, MSO, MÇ.

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REFERENCES

1. Mohamadi A, Googanian A, Ahmadi A et al. Comparison of surgical or nonsurgical treatment outcomes in patients with thoracolumbar fracture with Score 4 of TLICS: a randomized, single-blind, and single-central clinical trial. Medicine (Baltimore) 2018;97(6):e9842.

2. Kim BG, Dan JM, Shin DE. Treatment of thoracolumbar facture. Asian Spine Journal 2015;9(1):133-46.

3. Azam MQ, Sadat-Ali M. The concept of evolution of thoracolumbar fracture classifications helps in surgical decisions. Asian Spine J 2015;9(6):984–94.

4. Denis F. The three column spine and its significance in the classification of acute thoracolumbar spinal injuries. Spine 1983;8(8):817-31.

5. Gomleksiz C. Thoracolumbar fractures: a review of classifications and surgical methods. Journal of Spine 2015;04:250.

6. Vaccaro AR, Oner C, Kepler CK et al. AOSpine thoracolumbar spine injury classification system: fracture description, neurological status, and key modifiers. Spine 2013;38(23):2028-37.

7. Vaccaro AR, Schroeder GD, Kepler CK et al. The surgical algorithm for the AOSpine thoracolumbar spine injury classification system. Eur Spine J 2016;25(4):1087-94.

8. Kepler CK, Vaccaro AR, Koerner JD et al. Reliability analysis of the AOSpine thoracolumbar spine injury classification system by a worldwide group of naïve spinal surgeons. European Spine Journal 2015;25(4):1082–86.

9. Cheng J, Liu P, Sun D et al. Reliability and reproducibility analysis of the AOSpine thoracolumbar spine injury classification system by Chinese spinal surgeons. European Spine Journal 2016;26(5):1477-82.

10. Azimi P, Mohammadi HR, Azhari S et al. The AOSpine thoracolumbar spine injury classification system: a reliability and agreement study. Asian J Neurosurg 2015;10:282-5.

11. Abedi A, Mokkink LB, Zadegan SA et al. Reliability and validity of the AOSpine thoracolumbar injury classification system: a systematic review. Global Spine J 2019;9(2):231–42.

12. Reinhold M, Audigé L, Schnake KJ et al. AO spine injury classification system: a revision proposal for the thoracic and lumbar spine. Eur Spine J. 2013;22(10):2184–201.
13. Dodwad SN, Dodwad SJ, Wisneski R et al. Retrospective analysis of thoracolumbar junction injuries using the thoracolumbar injury severity and classification score, American spinal injury association class, injury severity score, age, sex and length of hospitalization. Journal of Spinal Disorders and Techniques 2015;28(7):410-6.
14. Schousboe JT. Epidemiology of vertebral fractures. Journal of Clinical Densitometry 2016;19(1):8-22.
15. Sidon E, Stein M, Ramalingam G et al. Gender differences in spinal injuries: causes and location of injury. Journal of Women's Health 2018;27(7):946-51.
16. Hernlund E, Svedbom A, Ivergård M et al. Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). Archives of Osteoporosis 2013;8:136.
17. Hoy D, Brooks P, Blyth F et al. The epidemiology of low back pain. Best Pract Res Clin Rheumatol 2010;24(6):769–81.
18. Rajasekaran S, Vaccaro AR, Kanna RM et al. The value of CT and MRI in the classification and surgical decision-making among spine surgeons in thoracolumbar spinal injuries. Eur Spine J 2017;26(5):1463–9.
19. Kepler CK, Vaccaro AR, Schroeder GD et al. The thoracolumbar AOSpine injury score. Global Spine Journal 2016;6(4):329-34.
20. Jordan KM, Cooper C. Epidemiology of osteoporosis. Best Practice & Research Clinical Rheumatology 2002;16(5):795-806.
21. Melton III LJ, Thamer M, Ray NF et al. Fractures attributable to osteoporosis: report from the National Osteoporosis Foundation. Journal of Bone and Mineral Research 1997;12(1):16-23.

ORIGINAL ARTICLE

EVALUATING THE EFFECTS OF NIGHT SHIFTS ON ATTENTION AND EXECUTIVE FUNCTION OF TRAKYA UNIVERSITY RESIDENTS USING THE TOWER OF HANOI TEST

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ABSTRACT

Aims: This study aims to evaluate the effects of night shifts on attention and executive function among residents working at Trakya University Hospital. ***Methods:*** This prospective study was performed between November 2019 – January 2020 on 83 residents working at Trakya University Hospital. The Tower of Hanoi test was used to measure the attention and function level of two different groups of residents. The first group being residents working with night shifts and the other group being residents with regular working hours. After the participants finished solving the puzzle, the number of moves and the finishing time were recorded. The demographic data about smoking, coffee intake, sleep hours, departments, and hand dominance were also recorded. ***Results:*** The participants were composed of 36 (43.4 %) female and 47 (56.6 %) male residents. The difference in smoking rate and sleep time between the two groups were found to be statistically significant whereas the difference between the completion time and moves was not statistically significant. ***Conclusion:*** Smoking and duration of sleep may affect the Tower of Hanoi puzzle performance. Although residents working with night shifts did not under-perform, the importance of sleep for cognitive skills such as attention and coordination cannot be underestimated. Stress caused by night shifts may affect reaction time for problem-solving, but further studies are needed. ***Keywords:*** Nightshift, attention, Tower of Hanoi test

INTRODUCTION

Nightshift is an irregular work schedule which is extended beyond the usual 08:00-17:00 working hours (1). This irregularity affects residents' lifestyles. Employees working with nightshifts, for instance, residents are more subjected to loss of sleep time, difficulties with sleep onset, drowsy driving, and difficulties with concentration (1). Furthermore, night shift work abolishes melatonin levels and causes repair decrement of oxidative DNA lesions which is suggesting a role for oxidative stress (1). Poor sleep quality was significantly associated with anxiety and depression (1). As the anxiety and depression levels increase, back problems, eyesight difficulties, ulcers, and migraine headaches may start to occur. Thus, the longer the residents work the more prone they become to under-performing in their daily tasks (2).

Night shifts are recognized as a burden that affects doctors' behavior and attitude (2). Night shift does not only affect the residents' stress levels, but it also affects their sleep cycles. Doctors usually have many duties during the night shifts and those duties interrupt their sleep cycles (1). Thus, residents working with night shifts experience desynchronosis. This is usually a result of disruption to the circadian rhythm which is a biological cycle to coordinate various behavioral and physiological activities (1).

The workload during the night shifts also leads to sleep deprivation which has a high incidence among doctors (3). The danger of sleep-deprived medical mistakes by health care professionals has been recognized (3). Gülser et al. (4) suggested that sleep disorders can be caused by night shifts since they cause interruption of the circadian rhythm. On the other hand, a study conducted by Baldwin et al. (2) states that longer or

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shorter sleep hours do not correlate with general health knowledge and attention. However short sleep periods relate the somatic symptoms such as "feeling run down" or "pain in the head" (2). For this reason, the necessity of sleep is very crucial for residents who need a lot of attention and coordination for their daily work.

"Tower of Hanoi" is used to measure the dysfunction and executive function levels. This measurement method is validated by a study on neuropsychology by Welsh et al (5). It is considered to be an exemplary measure of the executive function of the prefrontal cortex (5, 6). Solving the puzzle requires the coping ability with novel situations and means-end analysis (5). The puzzle also has an acceptable level of internal consistency (alpha=0.70) (5).

The aim of this study is to evaluate the effects of the night shift on attention and executive function among residents working at Trakya University Hospital using the Tower of Hanoi.

MATERIAL AND METHODS

This prospective study was approved by the Scientific Research Ethics Committee of Trakya University (Protocol Code: TÜTF-BAEK 2019-360). After obtaining informed consent from all participants, the study was performed between November 2019 and January 2020. The study population was composed of 83 residents who work at internal (cardiology, endocrinology, family medicine, gastroenterology, hematology, infectious diseases, internal medicine intensive care, nephrology, neurology, pediatrics, pulmonology, rheumatology) and surgical (anesthesiology, cardiovascular surgery, general surgery, gynecology, neurosurgery, ophthalmology, orthopedics and traumatology, otolaryngology, pediatric surgery, plastic surgery, urology) departments at Trakya University Hospital.

The trial was composed of two days. On the first and second days of trial, the residents were asked to solve the Tower of Hanoi puzzle and after they completed the puzzle, the number of moves and the completion time were recorded. The results from two different days with at least a 24-hour interval were evaluated to compare their performances. The puzzle trials were conducted in between 13:30-17:00 for each resident. On the second day of trial, data about their smoking habit, coffee intake, sleep duration, age, gender, department, shift status and hand dominance were recorded. Data on sleep duration, smoking habits, and coffee intakes are from the last 24-hours.

The participants were composed of two groups: residents with a night shift (continuously working for 36 hours) and residents with regular working hours (total of 9 hours). The first day of trial for the residents working on a night shift was before their night shift duty, and after they completed their night shift, they solved the puzzle again on their working hours. Residents on their regular working hours solved the puzzle in two different days with the same procedure.

"Tower of Hanoi" is a puzzle consisting of 3 bars (right, middle and left bars) and 5 different sized disks. The puzzle starts with all the disks being placed on the left bar. The aim of the puzzle is to take disks from the left bar and place them to the right bar. The person must build the tower on the right by following the three rules: only one disk can be moved at a time, a disk may not be placed on the table or held in the hand while another disk was being removed, a larger disk may not be placed on top of smaller disks (5). The mobile version of the puzzle has been used in this study.

For statistical analysis, SPSS 23.0.0.0 was used. The Kolmogorov-Smirnov test was used to check whether the variables distributed normally or non-normally. T-test was used for parametric variables whereas Mann-Whitney U test was used for non-parametric variables. Wilcoxon signed-rank test was used for evaluating the difference within the groups. The Chi-Square test was used for categorical descriptive data. Categorical variables were expressed as numbers and percentages. Normally distributed variables were summarized as mean and standard deviation, while non-normally distributed variables were summarized as median and interquartile range. In all statistical analyses, the significance level was determined as 0.05.

RESULTS

In this prospective study, the Tower of Hanoi test was performed on 83 residents and they were later divided into two groups; residents working on a night shift (n=40) and residents on their regular working hours (n=43). All steps in the puzzle and questionnaire were completed precisely. The total group was composed of 36 (43.4 %) female and 47 (56.6 %) male residents. The mean age of all participants was 27.9 ± 2.39 years. Comprehensive demographic data of the population can be observed in Table 1. Statistically significant difference was found in the smoking rate, and sleep time between groups (p=0.001).

Evaluation of the number of moves given by the digital Tower of Hanoi puzzle application and manu-

Table 1: Distribution of the residents according to their descriptive characteristics.

		Night shifts (n= 40)	Regular working (n= 43)	P value
Age (years)		27.83±2.1	28.05±2.6	0.952
Gender (n)	Female	14(35%)	22(51.2%)	0.136
	Male	26(65%)	21(48.8%)	
Smoking (n)	Yes	22	9	0.001
	No	18	34	
Coffee (n of cups)	Yes	33	39	0.269
	No	7	4	
Sleep time (hours)		4.88±1.42	6.62±1.45	0.001
Department (n)	Surgical	27	17	0.150
	Medical	13	26	
Hand dominance (n)	Right	38	39	0.677
	Left	2	4	

As descriptive statistics, quantitative data are expressed as mean ± standard deviation and qualitative data are expressed as numbers (percentages).

Table 2: Evaluation of moves and completion time.

		Night shifts (n= 40)	Regular working (n= 43)	P value
Moves (median (IQR))	1st	66 (44)*	69 (35)**	0.128
	2nd	70 (57)*	73 (44)**	0.538
Completion time, sec (median (IQR))	1st	153 (186)***	164 (197)****	0.307
	2nd	142.5 (93)***	142 (126) ****	0.841

*p=0.551: the difference between night shift groups in 1st and 2nd day.
**p=0.983: the difference between regular working groups in 1st and 2nd day.
***p=0.501: the difference between night shift groups in 1st and 2nd day.
****p=0.091: the difference between regular working groups in 1st and 2nd day.

Data are presented as median (interquartile range).

ally recorded completion time are presented in Table 2. Both of the groups, working with shifts and with regular hours, finished the puzzle with more moves on their second day of trial (p=0.551, and p=0.983, respectively). On the contrary, completion time records show a decrease on the second day of trial. Although there was no significant difference, residents working with shifts solved the puzzle with fewer moves on both of the days, and their completion time was also shorter on the first day of trial (p=0.128, p=0.583, and p=0.307, respectively).

DISCUSSION

Night shifts, especially in a demanding area like medicine, can be detrimental to physiological and psychological health. Healthcare professionals' attention and level of sleepiness may vary after shifts due to their working conditions. According to the literature, the Tower of Hanoi puzzle can be helpful to evaluate executive function which is of vital importance for doctors (5, 6). Their anticipation and problem-solving abilities were tested through the puzzle. Residents working with night shifts made fewer moves than residents working with regular hours. However, residents working with night shifts completed the task with more moves compared to their first trial when the test was performed after their night shifts. Residents who were working in regular hours also completed the task with more moves in their second trial. Besides, the completion time scores of both groups were quite close even though residents working with night shifts had a lesser time of sleep. This may be explained by a study conducted on mammals by Reser (7), stating that living in a stressful environment can cause changes in the body, notably in the neuroendocrine system. Humans and other mammals need to be more time-intensive and quick on information processing while under stress. This basic struggle for survival can be observed among residents. Poulton et al. (8) claimed that the lack of sleep and working conditions can cause stress, but it is not valid for every doctor.

The data obtained from this study shows that residents working with night shifts and residents working with regular hours completed the puzzle with more moves on their second day. However, Goel et al. (9) claimed that the Tower of Hanoi puzzle does not require planning abilities, therefore figuring out the trick of the puzzle is sufficient to complete the task. Both of the groups played and understood how to solve the puzzle on their first trial. On the second day of the study, two of the groups completed the puzzle with more moves. This data suggests that knowing how to solve the puzzle cannot be enough by itself, some external or internal factors may affect the results.

In our study, mean sleep time while working with a night shift was 4.88±1.42 hours, whereas the sleep time while working with regular hours was 6.62±1.45 hours for residents. Gülser et al. (4) confirms that restless legs syndrome which disrupts the circadian rhythm and night shift related sleep disorders can be seen among the health care workers. Our study does not include any scale to identify sleep disorders, but our results show a deficiency of sleep among the residents with night shifts. According to the literature, lack of sleep can cause stress which could increase vigilance, also lead to minor mistakes, tiredness, impaired decision-making, and poor performance on tasks (3, 7, 10, 11). In our study, the residents working on a night shift had fewer hours of sleep, and this situation might have affected the performance in a positive way which may be relevant to the stress caused by working conditions.

In addition to total sleep time, the smoking rate was also high among the residents with night shifts. Sleep time and smoking were confounding variables that may affect the number of moves and the completion time of the puzzle. According to the literature, nicotine influences the human brain in many ways including developed cognitive productivity, attention and memory in acute use (12). This cognitive development might lead the residents to solve the puzzle with fewer moves and time because of their accelerated information processing. Getting less sleep during the night shifts may be associated with not only the working conditions but also with smoking since nicotine alerts the brain in sensorial and motor aspects (12, 13). Although there was no significant difference found in regard to the residents' coffee consumption between the groups, caffeine may reduce reaction time and enhance performance. Buchvold et al. (14) states that on night shift duties, consumption of caffeine increases because of its stimulant effect. Our findings must be interpreted with caution because the number of cigarettes and the amount of coffee consumed daily were not included in the study. The amount of nicotine per cigarette varies for each brand. In addition, the amount of caffeine also varies regarding the cup size and coffee type. Amount and half-life of caffeine may affect attention span, therefore recording the time of the last coffee intake is recommended in future studies (13). According to the previous studies, although both caffeine and smoking have an impact on mental alertness, the effect that smoking has on cognitive skills should be evaluated with pre/post and acute/

chronic categories (12, 13). While acute smoking increases cognitive skills, long-term smoking is related to cognitive impairment (12).

The residents were chosen from two different departments: internal medicine and surgery. Within the groups, there was no significant difference in the number of residents between internal medicine physicians and surgeons. This data suggests that internal medicine physicians and surgeons might be distributed randomly in both of the groups. Wilkinson et al. (10) suggested that specialties with longer working hours are the ones who admitted low efficiency, but there was no distinctive analysis to compare surgery to internal medicine in our study.

In this study, there was no significant difference found in hand dominance between the night shift and regular working groups. Previous studies show that dominant hand preference affects attention (14,15). The relation of attention and right hemisphere dominance was shown by Weintraub et al. (15). A study conducted on the left and right-handed subjects by Chaudhary et al. (16) confirms that cognitive skills are related to hand dominance. The performances on attention and memory were found to be better in left-handed subjects (16). In our study, there were 2 left-handed subjects within residents working with night shifts and 4 left-handed subjects within residents working with regular hours. Since there were not many left-handed subjects involved in our study, it can be hard to establish extensive conclusions that evaluate the effect of hand dominance on the Tower of Hanoi performance. Additionally, we encourage conducting future studies that include one group of residents that are asked to solve the puzzle with their non-dominant hands, and another group of residents that are asked to solve the puzzle with their dominant hands. This selective use of hands may reveal varied results.

The Tower of Hanoi puzzle can determine whether a resident can solve problems quickly and if he/she has an advanced memory (17). There was no significant difference in the number of moves for the first and second days of residents working with night shifts and residents working with regular hours for both of the days. Both of the groups performed better on their first day of solving the puzzle which suggests that knowing how to solve the puzzle might not contribute to the subjects' performances on their second time of solving the puzzle. On the contrary, we found that the completion time was shorter when they performed the test for the second time. Residents working with night shifts completed the puzzle in 153 seconds on their first day and in 142.5 seconds on their second day. Residents working with regular hours completed the puzzle in 164 and 142 seconds on their first and second day, respectively. However, the difference between the completion times was not statistically significant. The stress factor or conditioning for doing no mistake in residents working with night shifts might be the reason for shorter completion time on the first day of the test. Completion time has shortened for both of the groups on the second day of the test. The completion time decreased by 11.5 seconds for the residents working with night shifts and 22 seconds for the residents working with regular hours. The reason behind a shorter completion time within the residents working with regular hours may be attributed to the difference in their sleeping hours. A smaller decrease in completion time was seen among the residents with night shifts which might be due to the elimination of the stress factor after finishing their night shift duty.

This study does not provide information about the impact of medications, and medical history on attention and sleepiness levels. Since the questionnaire was conducted participants' in their working space during office hours, they were not willing to answer personal and time-requiring questions, therefore we could not obtain enough data to analyze them. The subjects were chosen from the departments of surgery and internal medicine, but out of all residents, four of them were working on a shift in a different field rather than their expertise. Working in a different department and taking responsibility during the shifts may increase their level of stress which by implication can change the results. With more subjects, future studies evaluating the presented case are needed. Further studies with more subjects to determine if the Tower of Hanoi puzzle is reliable on measuring problem-solving speed on repetitive tests are recommended.

As a conclusion, smoking and duration of sleep were found to be different between the residents with night shifts and residents with regular working hours. This difference may have an impact on the number of moves and the time of completion. Even though residents working with night shifts did not perform worse than residents working with regular hours, the effects of night shifts on cognitive skills such as attention and executive function cannot be underestimated. Being exposed to stress during the night shift can decrease reaction time for problem-solving but further extensive studies are needed.

Ethics Committee Approval: This study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (Protocol Code: TÜTF-BAEK 2019-360).
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REFERENCES

1. Jaradat R, Lahlouh A, Mustafa M. Sleep quality and health related problems of shift work among resident physicians: a cross-sectional study. Sleep Med 2019;66:201-66.
2. Baldwin PJ, Dodd M, Wrate RW. Young doctors' health-I. How do working conditions affect attitudes, health, and performance? Soc Sci Med 1997;45(1):35-40.
3. Beecham L. Unanimous support for reduction in juniors' hours. Brit Med J 1989;298:121-3.
4. Gülser N, Öztürk L, Top MŞ et al. The relationship between restless legs syndrome and insomnia for the staff in shift. Archives of Neuropsychiatry 2012;49(4):281-5.
5. Welsh MC, Huizinga M. The development and preliminary validation of the Tower of Hanoi – revised. Assessment 2001;8(2):167-76.
6. Patsenko EG, Altmann EM. How planful is routine behavior? A selective-attention model of performance in the Tower of Hanoi. J Exp Psychol Gen 2010;139(1):95–116.
7. Reser JE. Chronic stress, cortical plasticity and neurocology. Behavioural Processes 2016;129:105-15.
8. Poulton EC, Hunt GM, Carpenter A et al. The performance of junior hospital doctors following reduced sleep and long hours of work. Ergonomics 1978;21(4):279-95.
9. Goel V, Grafman J. Are the frontal lobes implicated in "planning" functions? Interpreting data form the Tower of Hanoi. Neuropsychologia 1995;33(5):623-42.
10. Wilkinson RT, Tyler PD, Varey CA. Duty hours of young hospital doctors: Effects on the quality of work. J Occup Psychol 1975;48:219-29.
11. Lingenfelser TH, Kaschel R, Weber A et al. Young hospital doctors after night duty: their task-specific cognitive status and emotional condition. Medical Education 1994;28:566-72.
12. Campos MW, Serebrisky D, Castaldelli-Maia JM. Smoking and cognition. Curr Drug Abuse Rev 2016;9(2):76-9.
13. Ullrich S, de Vries YC, Kühn S et al. Feeling smart: effects of caffeine and glucose on cognition, mood and self-judgment. Physiol Behav 2015;151:629-37.
14. Buchvold HV, Pallesen S, Øyane NMF et al. Associations between night work and BMI, alcohol, smoking, caffeine and exercise – a cross sectional study. BMC Public Health 2015;15:1112.
15. Weintraub S, Mesulam M. Right cerebral dominance in spatial attention: Further evidence based on ipsilateral neglect. Arch Neurol 1987;44(6):621-5.
16. Chaudhary S, Narkeesh A, Gupta N. A study of cognition in relation with hand dominance. Journal of Exercise Science and Physiotherapy 2009;5(1):20-3.
17. Leana MZ. Üstün zekalı ve normal çocuklarda yönetsel fonksiyonlar: Londra Kulesi testi (dissertation). Istanbul: Istanbul Univ. 2005.

CASE SERIES

CLINICOPATHOLOGICAL FEATURES OF MYELOID SARCOMA PATIENTS FROM A SINGLE CENTER EXPERIENCE

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ABSTRACT

Aims: This retrospective study aims to emphasize clinicopathological data and diagnosis of an uncommon myeloid neoplasm; myeloid sarcoma. ***Methods:*** Data of all patients from 2000-2019 were retrieved from the archives of Trakya University School of Medicine Hematology and Pathology Departments. Patients' charts were examined retrospectively by collecting data including age, gender, anatomic site, history of hematological malignancy, blood count, pathological characteristics and treatments administered. ***Results:*** There were 8 patients; 6 male and 2 female. The median age was 42.5 years (range: 29-69 years). The most prevalently involved sites were skin, lymph node and bone/soft tissue. There were six patients as myeloid sarcoma with preexisting or concurrent acute myeloid leukemia, one patient as de novo and one patient as acute myeloid leukemia with myelodysplasia related changes. One of the concurrent acute myeloid leukemia patients was Down syndrome related acute myeloid leukemia with myeloid sarcoma. Immunohistochemically, out of 8 patients, 4 were of myelomonocytic, 2 were of the myelocytic and 2 were of the monocytic differentiation. ***Conclusion:*** Myeloid sarcoma is a tumor mass made up of immature myeloid blasts appearing at an anatomical site other than bone marrow. Taking into account of having a challenging diagnosis, unusual cellular infiltration at any site on a patient especially with a history of acute myeloid leukemia should have myeloid sarcoma in their differential diagnosis. ***Keywords:*** Myeloid sarcoma, acute myeloid leukemia, myeloid neoplasia

INTRODUCTION

Myeloid sarcoma (MS), also previously known as granulocytic sarcoma, is a rare condition characterized by the extramedullary proliferation of a tumor mass made-up of immature myeloid cells which may end up with the destruction of the tissue found (1). MS can be seen at any age having a slight male predominance. It is mostly reported to affect the skin, bone or lymph nodes, however, there have been sites submitted throughout the whole body (2). MS, for the most part, is detected concurrently in patients with acute myeloid leukemia (AML), it may additionally occur in other bone marrow diseases like myeloproliferative neoplasms (MPNs) or myelodysplastic syndrome (MDS) and de novo which is a very rare entity (3). On the other hand, in some cases, MS may be the first evidence of AML or be a manifestation of a previously treated AML patient in remission (4).

Even with the modern diagnostic techniques including flow cytometry and immunohistochemistry, the identification of MS can be difficult. Hence, patients with a history of myeloid neoplasia exhibiting atypical cellular infiltrate at any site should be a hint for MS (4).

In this study, eight patients with MS were retrospectively analyzed from a single center aiming to emphasize their clinicopathological data and facilitate the diagnosis of an uncommon myeloid neoplasm like MS.

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MATERIAL AND METHODS

Data of all patients from the years 2000-2019 were retrieved from the archives of the Trakya University School of Medicine Hematology and Pathology Departments. Patients' charts were examined retrospectively by collecting data including age, gender, anatomic site, history of hematological malignancy, blood count, pathological characteristics, and treatments administered. Hematoxylin and eosin (H&E) stained slides and immunohistochemistry stains were analyzed, including antibodies for myeloperoxidase (MPO), CD33, CD34, CD68, and CD117 for showing the blastic cells and myeloid differentiation.

RESULTS

In our study, out of 8 patients, 6 were male and 2 were female. The median age was 42.5 (range: 29-69 years). The most commonly involved sites were skin (n=3/8) and lymph nodes (n=2/8), other sites included bone/soft tissue (n=1/8), parotid gland (1/8), testicle (n=1/8) and rectum (n=1/8). Symptoms of the patients were in accordance with the sites involved. Regional pain, lymphadenopathy and mass were the most common findings. There were six patients as myeloid sarcoma with preexisting or concurrent acute myeloid leukemia, one patient as de novo and one patient as acute myeloid leukemia with myelodysplasia related changes. One of the concurrent acute myeloid leukemia patients was Down syndrome related acute myeloid leukemia with myeloid sarcoma (Table 1). One of our patients had multiple sites involved, he was first presented with an enlarged right cervical lymph node (LN) with the progression of the disease, he later on exhibited rectal involvement as well. The odd thing about this patient's history is that his LN expressed positivity for CD7, CD43, CD34, TdT with an extensive loss of T-cells which caused his initial diagnosis to be Precursor T-cell Lymphoblastic Lymphoma. With further analysis, his bone marrow biopsy revealed he had AML. Additionally, MPO and CD68 tests were performed to patients LN biopsy validating that his first presentation was actually an MS with a TdT, CD7 co-expression (Figure 2).

On H&E stained samples MS cells were characterized by diffuse infiltration of the tissue. Morphologically most cells were intermediate to large-sized, with abundant cytoplasm, large irregular contoured nuclei along with myeloblastic, myelomonocytic or monocytic differentiation. Remaining lymphoid tissue and, follicles were present in the LNs as well as normal tissue was present in the testes, parotid gland and skin (Figures 1, 3 and 5).

Median level for hemoglobin was 7.00 (range: 6.1-10.5 g/dL), whereas median level for white blood cells was 30,740 (range: 0,1-125,000). Median for platelet was 20.500 (range: 7,000-40,000). Our patients had MPO (n=6/8) possession the most, continuing with CD117 (n=4/8) and CD68 (n=4/8) (Figure 2, 4 and 6). Immunohistochemically, out of 8 patients, 4 were of myelomonocytic, 2 were of the myelocytic and 2 were of the monocytic differentiation (Table 2).

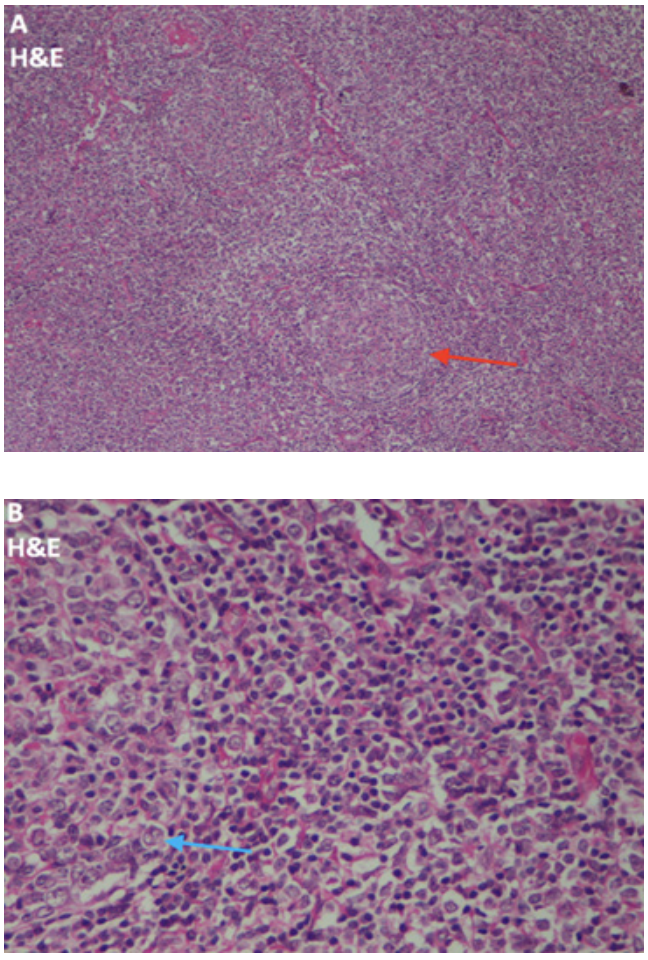

Figure 1: Case 4, lymph node involvement. A: Lymph node presenting atypical cell infiltration (blue arrow) between intact follicular structures (red arrow) (H&E, x100). B: High power examination shows diffuse infiltration of large blastic cells with clear cytoplasm (H&E, x200).

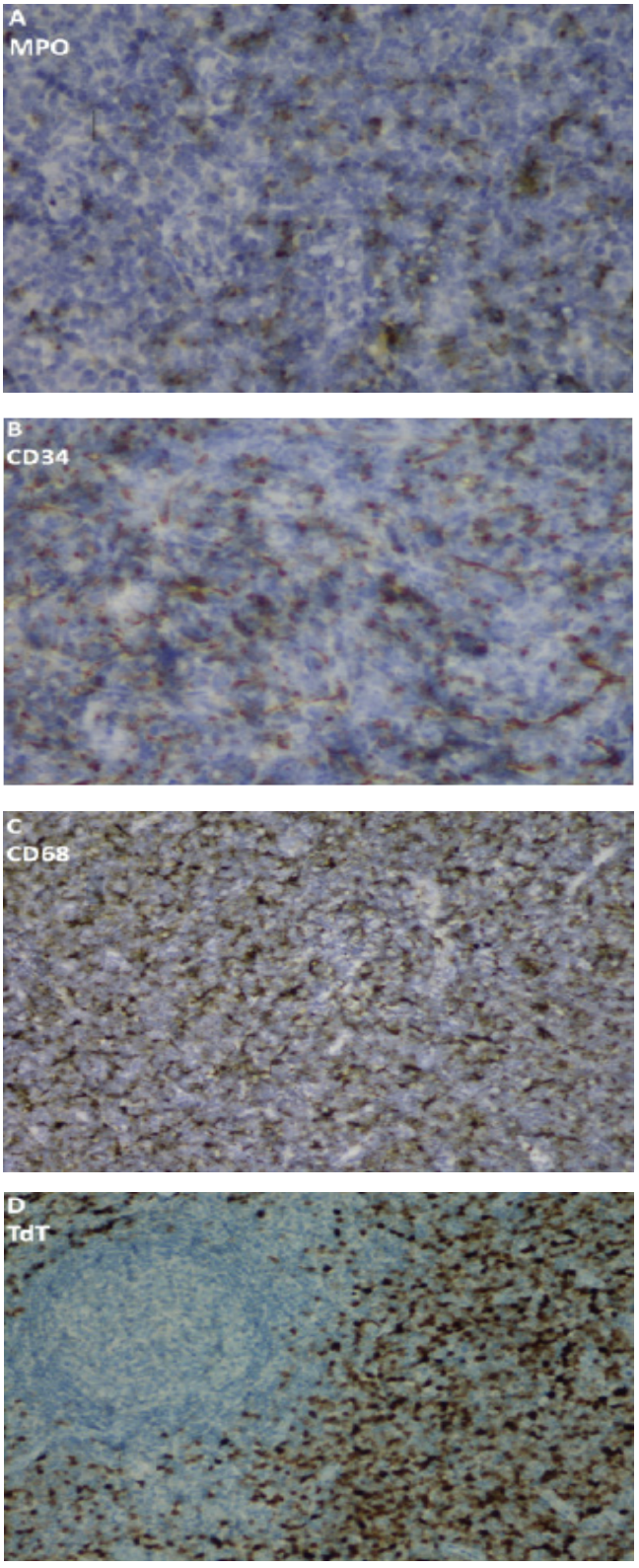

Figure 2: Immunohistochemistry of Case 4, lymph node involvement. A: Positive staining for MPO (x400). B: Positive staining for CD34 (x400). C. Diffuse positive staining for CD68 (x200). D. Diffuse positive staining for TdT on the blastic cells (x200).

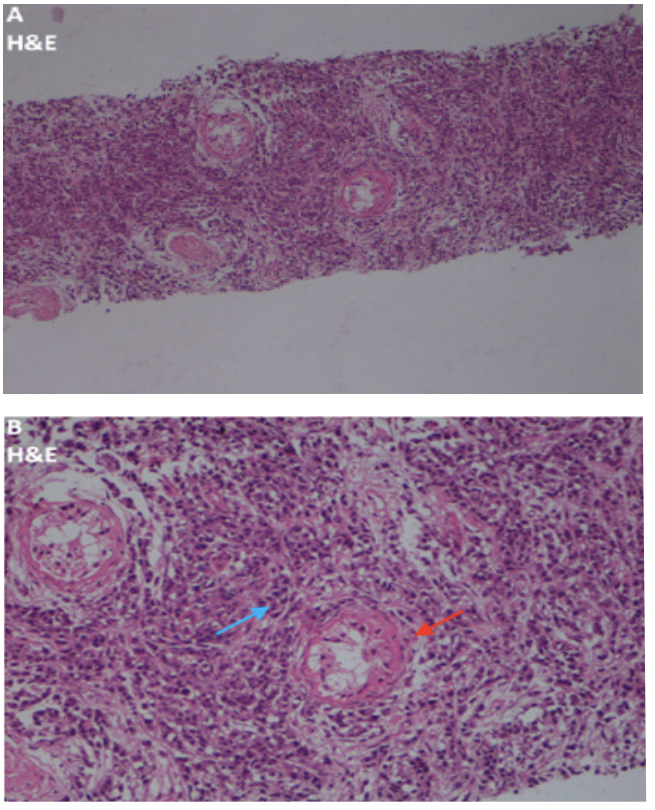

Figure 3: Case 3, testicular involvement. A: Diffuse blastic infiltration of testicular parenchyma (H&E, x100) B: High power examination of atypical cells surrounding (blue arrow) with abundant eosinophilic cytoplasm and pleomorphic/hyperchromatic nucleuses seminiferous ducts (red arrow) (H&E, x100).

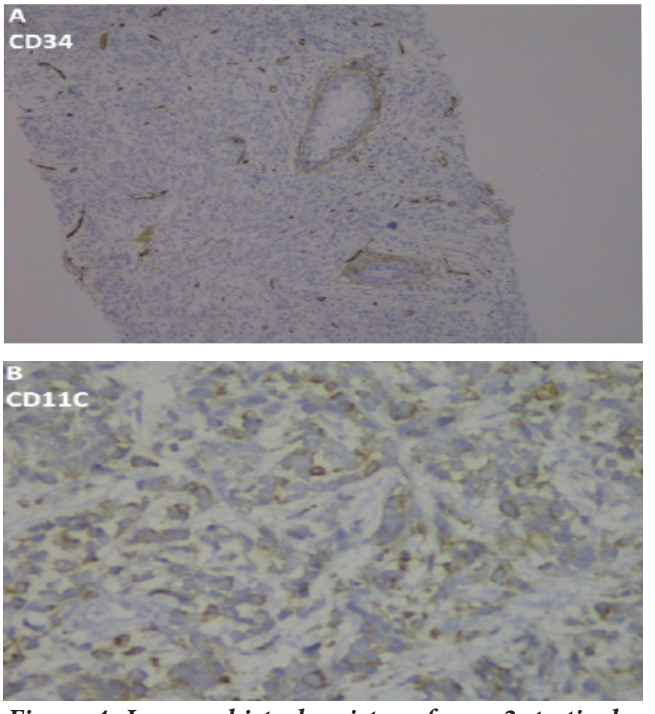

Figure 4: Immunohistochemistry of case 3, testicular involvement. A: Negative staining for CD34 (x100). B:Positive staining for CD11c (x400).

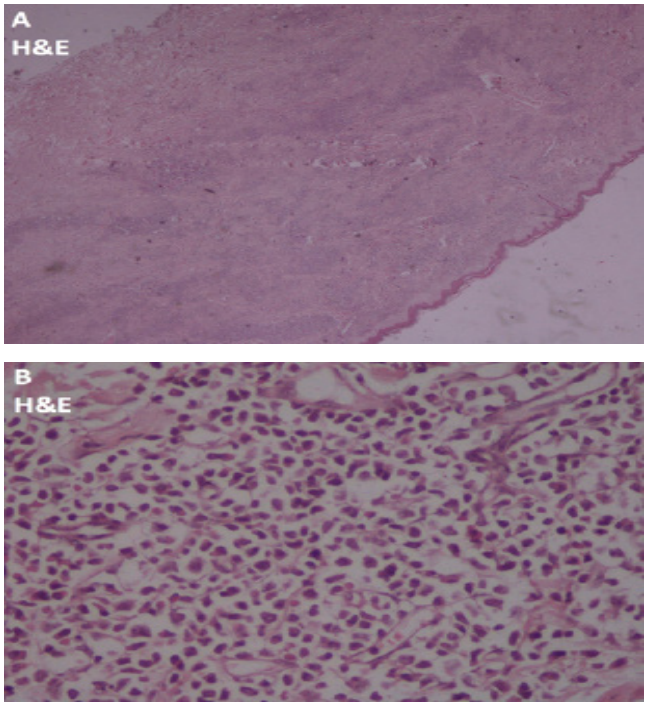

Figure 5: Case 2, skin involvement, A: Atypical cell infiltration in the dermis surrounding vascular and adnexal structures causing a detachment in collagen bands (H&E, x40). B: High power examination of monoblastic cells with eosinophilic cytoplasm and large nucleus (H&E, x400).

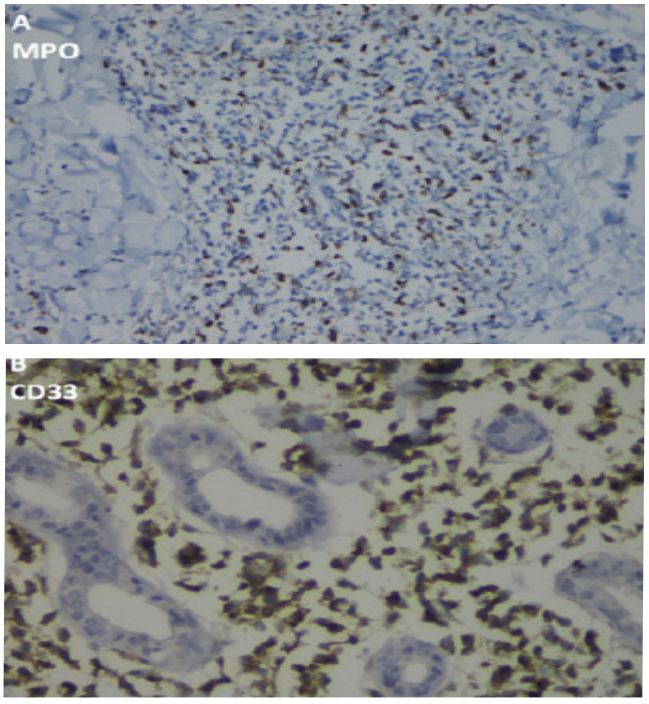

Figure 6: Immunohistochemistry of Case 2, skin involvement. A: Scattered positive staining for MPO (x200). B: Diffuse positive staining for CD33 (x400).

Our patients had MPO (n=6/8) positivity the most, continuing with CD117 (n=4/8) and CD68 (n=4/8) (Figure 2, 4 and 6). Immunohistochemically, out of 8 patients, 4 were of myelomonocytic, 2 were of the myelocytic and 2 were of the monocytic differentiation (Table 2).

Median level for hemoglobin was 7.00 (range: 6.1-10.5 g/dL), whereas median level for white blood cells was 30, 740 (range: 01-125,000). Median for platelet was 20.500 (range: 7,000-40,000).

Table 1: Clinical feature of patients.

Case	*Age/Gender*	*Involved Site*	*Clinical Manifestation*	*Associated Hematological Disorder*	*Systemic Treatment received*
1	35/M	Bone and Soft Tissue	Pain in left ankle	Concurrent AML	Remision induction 3+7 (Idarubicin+Cytosine arabinoside)
2	69/F	Skin	Ecimosis and Bullous Lesions on arms and legs	AML with Myelodisplasia related changes	4 cycles of azacitidine (due to MDS), 1 cycle of high dose Cytosine arabinoside
3	41/M	Testicle	Mass in right testicle	Concurrent AML	Remision induction 3+7 (Idarubicin+Cytosine arabinoside) 3 cycles of high dose Cytosine arabinoside, 1 cycle of FLAG-İda
4	58/M	LN (Primary IS)	Mass in right cervical LN	De novo	Remision induction 3+7 (Idarubicin+Cytosine arabinoside), 3 Cycles of high dose Cytosine arabinoside
		Rectum	Anal pain and mass in rectum		
5	29/M	Skin	Nodular lesion on left arm	Concurrent AML, AML induced hemophagocytic lymphohistiocytosis (HLH)	Remision induction 3+7 (Idarubicin+Cytosine arabinoside) 3 cycles of high dose Cytosine arabinoside, 1 cycle of FLAG-İda, Etoposide (due to HLH)
6	44/M	Parotid gland	Left preauricular mass	Down Syndrome Related Concurrent AML	Remision induction 3+7 (Idarubicin+Cytosine arabinoside) 3 cycles of high dose Cytosine arabinoside, 1 cycle of FLAG-İda
7	36/F	Skin	Lesion on left ankle	Concurrent AML	Remision induction 3+7 (Idarubicin+Cytosine arabinoside) 3 cycles of high dose Cytosine arabinoside
8	57/M	Lymph Node	Left axillar mass	Concurrent AML	Remision induction 3+7 (Idarubicin+Cytosine arabinoside) 3 cycles of high dose Cytosine arabinoside

***M:** Male, **F:** Female, **IS:** Involved Site, **LN:** Lymph Node, **AML:** Acute Myeloid Leukemia, **MDS:** Myelodysplastic Syndrome*

Table 2: Laboratory and Pathological features of patients.

Case	Routine Blood Test			Involved Site	IHC markers on MS biopsies
	Hb (g/dL)	WBC ($x10^3$)	Platelet ($x10^3$)		
1	10.2 g/dL	7,000	25,000	Bone and Soft Tissue	MPO, CD11c, CD33, CD34, CD68, CD117, Ki-67 70-80%
2	6.3 g/dL	44,000	23,000	Skin	MPO, CD11C, CD25, CD33, CD68, CD34, CD117, CD138
3	6.1 g/dL	125,000	7,000	Testicle	CD11C, CD117
4	10.5 g/dL	31,480	27,000	LN (Primary IS)	MPO, CD10, CD11C, CD20, CD33, CD68 TdT, Ki-67 70-80%
				Rectum	MPO, CD7, CD34
5	7.0 g/dL	0,1	10,000	Skin	CD68, CD117
6	7.1 g/dL	2,500	13,000	Parotid Gland	CD11C, CD33, CD34. CD68
7	6.9 g/dL	40,000	40,000	Skin	MPO, CD34
8	6.1 g/dL	30,000	18,000	Lymph Node	MPO, CD34

Hb: *Hemoglobin,* ***WBC:*** *White Blood Cell,* ***IS:*** *Involved Site,* ***LN:*** *Lymph Node,* ***IHC:*** *Immunohistochemistry,* ***MS:*** *Myeloid Sarcoma*

DISCUSSION

Myeloid sarcoma is a rare myeloid neoplasm presented as a tumor mass made up of immature myeloid blasts localised at an anatomical site other than bone marrow. Broad classification for MS according to the European Society for Hematology may ocur in the following circumstances: 1. concurrent with AML; 2. extramedullary relapse of AML or following a bone marrow transplantation; 3. occurring with other MPNs including CML, MDS or bone marrow fibrosis; and 4. isolated MS which has normal bone marrow biopsy and blood count lacking any history of myeloid neoplasia (4). Likewise, in our study, 7 patients out of 8 developed MS concurrent with AML, and one patient exhibited MDS at the beginning of the disease, later on, turned into AML also having a manifestation of MS. Békássy et al.'s (5) retrospective analysis of 5824 patients who underwent hematopoietic stem cell transplantation (HSCT) for AML, CML or MDS from 1981 to 1992, found that 26 of the patients had evidence of MS.

The etiology of MS remains ambiguous; therefore, diagnosis may be challenging. Patients' clinical features, radiology findings, immunohistochemistry, and cytogenetic features should evaluated for a more accurate diagnosis. For visualization techniques, Positron Emission Tomography/Computed Tomography has been shown to be more beneficial in the localization of tumors (6). Radiologically guided core biopsy, which offers more reliable results, should be performed, rather than traditional fine-needle aspiration biopsy (7). H&E stained slides usually reveal infiltrating myeloid cells at different stages of maturation possessing either granulocytic or monocytic maturation, also seen in AML. With the purpose of making a more reliable diagnosis; immunohistochemistry, flow cytometry, fluorescence in situ hybridization (FISH), real-time protein chain reaction analysis, and next-generation sequencing have been shown to increase the accuracy (1, 4).

A systematic review carried out by Magdy et al. (8) reported similar immunohistochemical results with ours; MPO, CD34, CD68, CD117, and lysozyme were the most common antigens possessed. In comparison with other retrospective studies; skin, LN, bone, soft tissue, and gastrointestinal tract are the most commonly involved sites which correlate with our results as well (1, 9).

Along with a known poor prognosis, there still hasn't been a large prospective study conducted to report the actual prognosis for MS. It may depend on tumor location, genetics, the stage at diagnosis, and treatment strategy. It is usually known to be 10 to 12-month period, with rare reported cases over >16 years of follow-up (3, 10). However, a bigger study done by Movassaghian et al. (11) revealed a higher 3-year survival. Site involved had an important impact on the survival with better reported prognosis for isolated MS sites involving gastrointestinal mucosa, pelvis, eyes/gonads (11). On the contrary, patients with isolated MS report a longer overall survival (3). Pileri et al. (1) attempted to identify poor prognostic factors by showing that neither disease course nor answer to therapy are influenced by location, age, being concomitant with AML or not, and morphology. Interestingly CXCR4 protein determined by immunohistochemistry was related to increased overall survival in a recent study done by Kawamoto et al. (12).

Misdiagnosis frequently occurs and needs to be differentiated from non-Hodgkin lymphomas, histiocytic lymphoma, mucosa-associated lymphoid tissue lymphoma, anaplastic large-cell lymphoma (ALCL), lymphoblastic lymphoma/leukemia (LBL), melanoma, Ewing sarcoma, and thymoma. Having similar morphological findings like diffuse infiltration of tumor cells, MS has immature granulocytic infiltration being negative for CD3, CD20, CD79a, and PAX-5 and positive for myeloid differentiation antigens (3, 8). The most common misdiagnosis usually happens between LBL/leukemia and ALCL, starry sky appearance with a lack of nucleolus for LBL/Leukemia and CD30 positivity for ALCL are helpful morphological characteristics for differentiation (3). Since MS may have coexpression of T-cell markers, immunohistochemical expression of MPO, lysozyme, CD34, CD68, and CD117 should be analyzed with a bone marrow biopsy for AML to verify your results (9). Given that one of our patients had an MS with the coexpression of Tdt and T-cell markers.

When it comes to treatment strategies due to deficient prospective studies, there still has not been a proper chemotherapy protocol developed for MS. According to patient's age, performance, and underlying disease (de novo, secondary to AML, secondary to MDS, etc.), treatment protocol can vary from induction, consolidation salvage chemotherapy and/or to allogenic HSCT depending on degree of patient's suitability, on a side note addition of clinical studies testing monoclonal antibody for treating MS are still ongoing (3). After the disease is under control, local therapy including surgery and radiotherapy simultaneously may be performed on sites with MS involvement, which have been demonstrated in retrospective studies to not affect overall survival and prognosis (3).

In conclusion, MS which is an uncommon diseases should be taken into consideration as a differential di-

agnosis of any unusual cellular infiltration at any site, particularly if a patient has a history of AML. Comprehensive diagnostic work-up and comprising genetic profile should be done in all cases. Earlier induction therapy may result in better outcomes, furthermore, prospective multicenter controlled trials that integrate novel targeted therapies for refining and taking one step closer to better understanding the disease are needed.

Ethics Committee Approval: N/A

Informed Consent: Informed consents were obtained from patients for this study.

Conflict of Interest: The authors declared no conflict of interest.

Author contributions: Concept: FEA, OPF, KHO Design: FEA, OPF, KHO Supervision: FEA, OPF, EM, KHO Resources: FEA, OPF, EM, KHO Materials: FEA, OPF, EM, KHO Data collection and/or processing: FEA, OPF, EM, KHO Analysis and/or Interpretation: FEA, OPF, EM, KHO Literature Search: FEA, OPF, KHO Writing Manuscript: FEA, OPF, KHO Critical Review: FEA, OPF, KHO

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REFERENCES

1. Pileri SA, Ascani S, Cox MS et al. Myeloid sarcoma: clinico-pathologic, phenotypic and cytogenetic analysis of 92 adult patients. Leukemia 2007;21(2):340-50.

2. Claerhout H, Sophie Van Aelst S, Melis C et al. Clinicopathological characteristics of de novo and secondary myeloid sarcoma: a monocentric retrospective study. Eur J Haematol 2018;100(6):603-12.

3. Wilson CS, Medeiros LJ. Extramedullary manifestations of myeloid neoplasms. Am J Clin Pathol 2015;144(2):219-39.

4. Almond LM, Charalampakis M, Ford SJ et al. Myeloid sarcoma: presentation, diagnosis, and treatment. Clin Lymphoma, Myeloma Leuk 2017;17(5):263-7.

5. Békássy AN, J Hermans J, Gorin NC et al. Granulocytic sarcoma after allogeneic bone marrow transplantation: a retrospective European multicenter survey. Acute and Chronic Leukemia Working Parties of the European Group for Blood and Marrow Transplantation. Bone Marrow Transplant 1996;17(5):801-8.

6. Stolzel F, Rollig C, Radke J et al. F-FDG-PET/CT for detection of extramedullary acute myeloid leukemia. Haematologica 2011;96(10):1552-6.

7. Campidelli C, Agostinelli C, Stitson R et al. Myeloid sarcoma: extramedullary manifestation of myeloid disorders. Am J Clin Pathol 2009;132(3):426-37.

8. Magdy M, Abdel Karim N, Eldessouki I et al. Myeloid sarcoma. Oncol Res Treat 2019;42(4):219-24.

9. Kaygusuz G, Kankaya D, Ekinci C et al. Myeloid sarcomas: a clinicopathologic study of 20 cases. Turk J Haematol 2015;32(1):35-42.

10. Yamauchi K, Yasuda M. Comparison in treatments of nonleukemic granulocytic sarcoma: report of two cases and a review of 72 cases in the literature. Cancer 2002;94(6):1739-46.

11. Movassaghian M, Brunner AM, Blonquist TM et al. Presentation and outcomes among patients with isolated myeloid sarcoma: a Surveillance, Epidemiology, and End Results database analysis. Leuk Lymphoma 2015;56(6):1698-703.

12. Kawamoto K, Miyoshi H, Yoshida N et al. Clinicopathological, cytogenetic, and prognostic analysis of 131 myeloid sarcoma patients. Am J Surg Pathol 2016;40(11):1473-83.

CASE REPORT

ARROW CAUSE OF ANGINA PECTORIS: SINGLE CORONARY ARTERY ANOMALY IN ELDERLY PATIENT

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ABSTRACT

Aims: Coronary artery anomalies are rare diseases among the population. These anomalies, which are usually noticed by chance, can remain silent for many years without symptoms. We aimed to present a patient with a coronary artery anomaly without having any symptoms for many years. ***Case Report:*** A 73-year-old female patient presented to the Department of Cardiology of the Trakya University School of Medicine. The patient stated that she had chest pain that decreased with rest and increased with exercise for the last 2 months. After the cardiac examination of the patient, imaging procedures were deemed necessary. After imaging, the patient was diagnosed with a single coronary artery anomaly. The patient was recommended to have surgery, but she refused. Upon this, the patient was discharged on condition that she was kept under frequent follow-up. ***Conclusion:*** Coronary artery anomalies have reached higher rates of diagnosis thanks to increased imaging technologies in recent years. If these congenital diseases that can even cause death are noticed early, there are various treatment options. First of all, medical treatment is preferred, and surgery is recommended in patients with no response to the medical treatment. This disease, which is closely related to the patient's life, should be carefully evaluated by the doctors. ***Keywords:*** Coronary arteries, cardiac anomaly, angiography

INTRODUCTION

Coronary arteries are the vessels that nourish the heart and provide oxygen for its function. In a normal person, the coronary vessels originate from 2 main sources, right and left, and branch through the entire heart. If coronary arteries are anatomically different from normal population, it is called coronary artery anomaly. In single coronary artery cases, the right and left coronary arteries emerge from a single origin and then divide into two as of right and left, unlike the normal anatomical structure (1).

Coronary artery anomalies (CAA) are congenital defects. They are usually silent but with the development of technology, the use of coronary angiography has increased significantly. Therefore, coronary artery anomalies became more diagnosable (2).

Coronary artery anomalies are seen rarely in the population. Some of them may not cause clinical symptoms, whereas some of them do start with cardiac symptoms and may lead to death.

Abnormal development of the coronary vessels in the embryonic period causes coronary anomalies. These anomalies can often remain silent for many years without any symptoms, and can sometimes be detected incidentally while investigating for other diseases (2).

According to the current data, the frequency of coronary artery anomalies vary between 0.6-1.6% (3). This wide range between the values is due to the lack of a general definition that includes the variations of the coronary artery anomalies (3). Single coronary artery anomaly is the rarest one of these anomalies and its incidence decreases to 0.024-0.44% (4).

CAA can be classified into several parameters. These are listed as the location of the right or left sinus originates from Valsalva, the anatomical distribution on the surface of the ventricle, and its relationship with the aorta and pulmonary arteries. One of the methods used

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in the angiographic classification of CAA is Modified Lipton Classification (5).

Approximately 40% of the single coronary artery anomaly (SCAA) cases are seen with other cardiac anomalies. The most common of these have been reported as congenital heart diseases such as Fallot tetralogy, pulmonary atresia, persistent truncus arteriosus and transposition of the great arteries (4).

SCAA rarely presents with symmptoms such as myocardial ischemia, angina, syncope, and myocardial infarction. These symptoms may not be diagnostic for SCAA, but they direct us towards SCAA (6).

Apart from the anomaly, the patient's concomitant cardiac and non-cardiac diseases, lifestyle and daily activities shape the clinical course and prognosis of CAA.

We aim to present a case report regarding a patient with a coronary artery anomaly and contribute to the literature because of its rareness and potential death risk.

CASE REPORT

A 73-year-old female patient applied to the cardiology department of Trakya University School of Medicine with the complaint of chest pain that appears with effort and decreases while resting for the last 2 months. The first medical approach was electrocardiography (ECG) to determine our patient's medical condition. No abnormalities were detected on ECG. Additionally, the patient was evaluated by using an echocardiogram. In the echocardiogram, the ejection fraction value of the patient was 62%. In addition, the inferior wall was detected mildly hypokinetic. After these findings, it was necessary to perform coronary angiography. In the imaging, it was seen that the entire coronary system of the patient's heart was originated from the right coronary artery. However, no stenosis was observed in the vessels. For further examination, the patient also had a computerized tomography coronary angiogram. In the imaging, the left main coronary artery was seen between the aorta and the right ventricular outflow tract (Figure 1, 2).

After the evaluation, the option to have surgery was offered to the patient, but she did not accept the surgery. Upon this, the patient was prescribed 50 mg of metoprolol, 20 mg of atorvastatin, 20 mg of acetylsalicylic acid. After the treatment, doctors decided to keep the patient under supervision with regular visits. Lastly, the patient was informed about the risks and she was discharged.

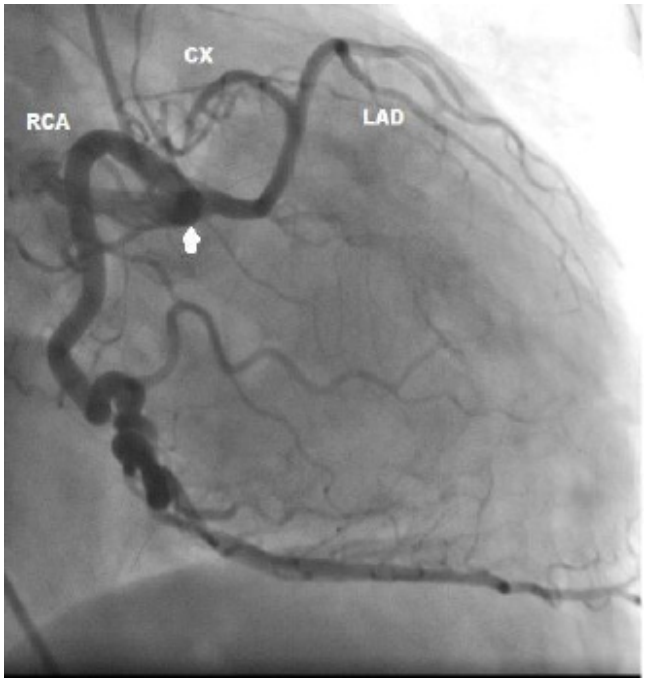

Figure 1: Coronary angiography view: Right oblique window (RCA: Right coronary artery, LAD: Left artery descending, CX: Circumflex).

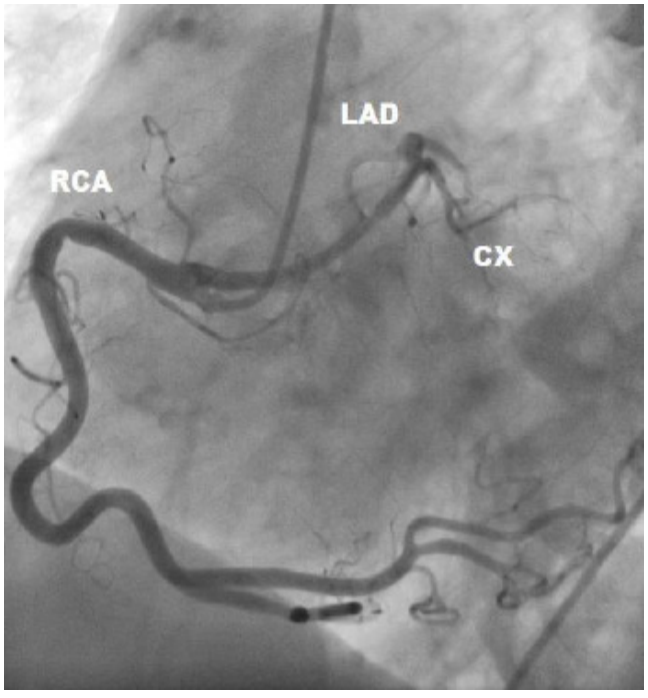

Figure 2: Coronary angiography view: Left oblique window (RCA: Right coronary artery, LAD: Left artery descending, CX: Circumflex).

DISCUSSION

The incidence of CAA varies depending on the sources. Çayhan et al. (7) stated the range is between 0.2-1.2 . Although these anomalies are seen rarely, there are cases in the literature that cause myocardial dysfunction, infarction, syncope, angina and sudden death (7, 8).

Patients with CAA are generally detected incidentally and do not differ significantly from normal hemodynamic parameters. However, CAA with an ectopic origin and passing through the aorta and pulmonary arteries have a higher potential to cause myocardial ischemia and even sudden death (2).

Coronary artery anomalies can basically be divided into 3 main categories. These are exit anomalies, cruise anomalies, and termination anomalies. It is possible to divide these 3 types into subtypes. There is not a certain classification in the literature thus there are different perspectives in many articles (2, 3). Our case falls under the coronary exit anomaly category because of its anatomical structure. It is possible to classify the coronary artery exit anomalies into 3 groups according to the osteal location and the number of ostia (2, 3).

In our case, the entire coronary system originates from the right coronary artery. In other words, the left main coronary artery originates from the sinus of Valsalva.

Usually, many types of CAA's do not have life-threatening complications. They may remain silent for many years and even may not cause symptoms until the end of life. The fourth type, unlike the others, has a risk of angina, myocardial infarction and sudden cardiac death. Due to these risks, surgical treatment is recommended for type 4 patients (5).

Arrhythmogenic right ventricular dysplasia and hypertrophic cardiomyopathy are accepted as the most common causes of sudden cardiac death and coronary artery anomalies are the third right after them (3). Although Güven et al. (4) indicate that the coronary artery anomalies are one of the reasons for sudden cardiac death at a young age, our case is 73 years old and has not shown any life-threatening symptoms like angina or dyspnea until this time.

Early diagnosis and drawing a road map according to the anatomical structure of the anomaly are the golden steps in the treatment process. In diagnosis, conventional cardiac angiography is accepted as the gold standard. However, in recent years, computerized tomography coronary angiogram has been the most used and recommended method due to its definitive diagnostic ability (3).

Symptomatic patients are mostly related to the size of myocardial tissue at risk and the character of the anatomy (4-6).

As a conclusion, CAA can be very serious and remain silent for years. These congenital anomalies, which can affect the patients' quality of life and cause them to die at a younger age, should not be overlooked in patients with compatible cardiac symptoms.

Ethics Committee Approval: N/A

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REFERENCES

1. Sharma B, Chang A, Red-Horse K. Coronary artery development: Progenitor cells and differentiation pathways. Annu Rev Physiol 2017;79:1-19.
2. Göldeli Ö, Badak Ö, Kırımlı Ö. Tek koroner arter: Olgu sunumu. Turk Kardiyol Dern Arş 1999;27:647-51.
3. Çelik A, Doğdu O, Özdoğru İ et al. Single coronary artery. Turk Kardiyol Dern Ars 2009;37(8):591.
4. Güven A. Single coronary artery anomaly: A report of two cases. Turkiye Klinikleri J Cardiovasc Sci 2013;25(2):84-7.
5. Başar N, Akpınar İ, Turak O et al. Frequency of isolated single coronary artery anomalies during conventional coronary angiography. Selçuk Ünv Derg 2011;27(3):137-41.
6. Kandemir H, Alp Ç, Karadeniz M et al. Tek koroner arter çıkış anomalisi: Olgu sunumu. Ortadoğu Tıp Dergisi 2018;10(2):205-8.
7. Çayhan B, Taş S, Saçlı H et al. Koroner arter anomalili bir olguda cerrahi tedavi. Kosuyolu Kalp Dergisi 2014;17(1):76-8.
8. Alpsoy Ş, Akyüz A, Akkoyun D et al. Sağ sinüs valsalvadan çıkan sol ana koroner arter anomalisi. Kocatepe Tıp Dergisi 2016;17(1):1-4.

TMSJ
REVIEW

IL-17/TNF-α BISPECIFIC ANTIBODIES AS NEW THERAPEUTIC APPROACH TO RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid arthritis is a systemic autoimmune disease characterized by chronic inflammation causing swelling in the joints. IL-17/TNF-α bispecific antibodies are antibodies that can bind to two different types of epitopes and work on two different types of receptors. IL-17/TNF-α bispecific antibodies have anti-inflammatory effects that act by blocking the inflammatory pathways of rheumatoid arthritis. Thus, bispecific antibodies have the potential to be the latest effective therapy against rheumatoid arthritis.

Keywords: Bispecific antibodies, rheumatoid arthritis, therapeutics

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammation causing swelling in the joints (1). The characteristics of RA include swollen joints (commonly small joints of the hands and feet) and pain due to this swelling. On physical examination, RA presents with swellings, warmth, and stiff joints. Initially, the pain in the joints will disappear within a few minutes, but long-term RA can cause prolonged joint pain and joint damage. These symptoms can be caused due to autoimmune reactions in synovial tissue. Damage to the joints results in physical limitations and joint pain because of the degenerative changes in cartilage (2).

PATHOGENESIS OF RHEUMATOID ARTHRITIS

Joint damage in RA starts by macrophage proliferation triggered by autoimmune factors, Porphyromonas, gingivitis infections, Epstein-Barr virus, cytomegalovirus or due to the smoking pollution of the environment. These factors can trigger the process of citrullination which is the conversion of arginine into citrulline. The presence of citrulline results in loss of tolerance in T cells and B cells and attacks the synovial tissue of the joints using macrophages (3, 4). Naive and memory B cells infiltrate the synovial tissue of the joints, resulting in continuous and further activation of B cells. Continuous activation of B cells produces pro-inflammatory cytokines such as tumor necrosis factor (TNF) -α and chemokines. Memory B cells, differentiated from immature B cells, can produce autoantibodies (3, 5).

T cells play a role in the development of RA through T-helper (Th) 17 cells that produce IL-17 (6). Increased level of IL-17 production enhances the activity of fibroblast-like synoviocytes (FLS) which stimulate the production of matrix metalloproteinases (MMP), pro-inflammatory cytokines, intracellular adhesion molecule-1 (ICAM1) and vascular cell adhesion molecule-1 (VCAM-1), resulting in chronic inflammation of the joints. FLSs also activate osteoclastogenesis, a process that triggers joint damage (4). These inflammatory activities eventually cause damage to the cartilage and bone. Cartilage damage is the result of the activity of FLS to form MMP, which causes damage to connective tissue type II collagen and decreases the effectivity of inter-joint lubrication (7). Damage to the bone is the result of macrophages activating the Nucleus Factor-κ light chain enhancer B cell (NF-κB) receptor to stimulate osteoclast activity causing bone erosion (3).

Bearing in mind its pathogenesis, RA requires articulate treatment plans that focus on its complex inflammatory reactions. Proinflammatory cytokines IL-17 and TNFα have important roles in the development

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of rheumatoid arthritis and can be used as therapeutic targets for RA treatments.

BISPECIFIC ANTIBODIES

Bispecific antibodies (bsAbs) are antibodies that can bind to two different types of epitopes so that they can be used for different signaling (8). Bispecific antibodies can be produced by three different processes, which are; chemical conjugation, fusion of two different hybridoma lines and through recombinant DNA utilization with a genetic approach. The fusion of two different hybrids produces hybrid-hybridomas that produce heterogeneous antibodies which include bsAbs (9). However, the bsAbs can also be produced by chemical conjugation using two IgG molecules or two antigen-binding molecules (10).

The structure of bsAbs consists of 1-4 polypeptide chains which are composed of antibody components that have a component of the drug that has high-temperature reserves, high solubility, high chemicals, and low viscosity (11). Bispecific antibodies were developed from Chinese hamster ovary cells (CHO) and Escherichia coli bacteria as host systems that have been used in biopharmaceutical technology for a long time (11, 12). The bsAb activity has the effect of cytotoxicity resolution through the complement system and phagocytosis to target cells through antibodies. Taking into account the mechanisms of inflammatory diseases, bsAbs have a high effect on cytokines and chemokines in vivo through targeting the inflammatory response so that it can reduce the secretion of bone reducing substances through FLS (13).

Bispecific antibodies have a short half-life due to not having a crystallized fragment that binds to the salvage receptor that allows IgG to remain at high levels (11, 14). Therefore, bsAbs are combined with a protein from the crystallized fragment (Fc) constant in IgG which has an important role in the development of diseases related to interactions between proteins, ligands, and receptors and the complexity of pathological diseases. The use of a constant Fc domain of IgG which plays a role in the process of recycling endosome degradation can bind to neonatal Fc receptors (FcRn) so that bsAbs have a longer half-life and lower renal clearance (15).

The utilization of bsAbs has many advantages. Some of these advantages are; ability to bind to the appropriate target cell, having adaptable components specific to disease conditions, and capabilities obtained through an easy prokaryotic disclosure system and eukaryotes (10). High specificity is one of the most crucial advantages of bsAbs. Since the molecule can bind to two distinct receptors, it can increase the antiproliferative effect of proinflammatory cells and increase the production of proinflammatory cells simultaneously (16).

BISPECIFIC ANTIBODY ACTIVITY IN RHEUMATOID ARTHRITIS

The activation of proinflammatory cytokines IL-17 and TNF-α are independent of the pathogenesis of RA, however, either cytokine can be found in the joint tissue of RA patients. Both cytokines act as inflammatory mediators. Bispecific antibodies block the IL-17 and TNF-α pathways and reduce rheumatic symptoms in patients who have resistance to monoclonal antibody treatment. The activity of bsAbs also inhibits the production of other cytokines that are influenced by the activity of cytokine IL-17, such as IL-6 and IL-8 (17). Cytokine IL-17 pathway also plays a role in FLS activation which stimulates the production of MMP-1 and MMP-13 showing that IL-17 has a role in chronic inflammation in the joints (18).

Rheumatoid arthritis is exacerbated by the interactions of FLS and macrophages which trigger chemoattractant secretions such as Chemokine C-X-C motif Ligand 1 (CXCL1), CXCL2, CXCL6 and Chemokine C-C motif ligand (CCL) 2, resulting in synovial hypoxia. The hypoxia condition in the synovial tissue will produce hypoxia-inducible transcription factor (HIF) -1a and will trigger the production of vascular endothelial growth factor (VEGF) which is a stimulus for angiogenesis (19).

The duality of the structure of bsAbs allows for further reduction in the inflammatory response, preventing the secondary joint damage. In addition, bsAbs play a role in preventing the production of FLS by inhibiting the activity of cytokines IL-17 and TNF-α. Through this inhibition of FLS, chemokine production is blocked to reduce the joint damage. This method of treatment can prevent the local destruction of bone and show no adverse effect on the rest of the immune system (19). However, the findings of Xu et al. (17) show that the effects of bsAbs are not so different from the effects of monoclonal antibodies (mABs) that work with two targets. Nevertheless, using bsAbs can reduce the economic burden of RA patients since they are more affordable compared to mABs (17).

Based on the research conducted by Liu et al. (20), the use of bsAbs that target both TNF- α and IL-17, reduces joint destruction and inflammation induced by RA in rats compared to the use of bsAbs etanercept with dose of 3 mg/kg and etanercept dose of 3 mg/kg for 3 weeks. Inhibition of TNF-α and IL-17 pathways,

also inhibit FLS formation by lowering MMP-3 levels and IL-6 levels which result in reduced osteoclast levels and their activity. Overall, this activity of molecules reduces bone erosion and maintain bone homeostasis by increased osteoblast activity and increased osteocalcin levels. Based on the research conducted by Fischer et al. (21), giving bsAbs for the treatment of RA is more effective than using a single dose of mABs.

Bispecific antibodies are known to have better long-term therapeutic effects on RA compared to monoclonal antibodies. Findings of Alzabin et al. (22) show an increase in the severity of RA's prognosis when given a single TNF-α inhibitor after 15 days of discontinuation of therapy and a single IL-17 after 30 days of treatment interruption. Rats that have taken TNF-α and IL-17 bsAbs inhibitors can recover from RA after routine administration for 40 days and show a decrease in antigen-specific response thus providing a protective effect on the joints.

CONCLUSION

Rheumatoid arthritis is an autoimmune disease characterized with chronic inflammation of joints presenting with pain and swelling of the affected joints. Currently, therapies target the pathogenesis of RA to reduce the activity of inflammation in the joints. Bispecific antibodies can target two proinflammatory cytokines that can inhibit the activity of joint damage by proinflammatory cytokines. IL-17/TNF-α bispecific antibodies have higher effectiveness compared to monoclonal antibodies to achieve the cure target of rheumatoid arthritis therapy.

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Informed Consent: N/A

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Author contributions: Concept: MLA. Supervision: MLA. Resources: MLA. Materials: MLA. Data collection and/or processing: MLA. Analysis and/or Interpretation: MLA. Literature Search: MLA. Writing Manuscript: MLA. Critical Review: MLA.

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REFERENCES

1. Sridhar R, Ramya SS, Sowjanya S. Rheumatoid arthritis - a review. World J Pharm Pharm Sci 2016;5(10):1283–302.

2. Xu B, Lin J. Characteristics and risk factors of rheumatoid arthritis in the United States: An NHANES analysis. PeerJ 2017;24(5).

3. Mcinnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365(23):2205–19.

4. Cooles FA, Isaacs JD. Pathophysiology of rheumatoid arthritis. Curr Opin Rheumatol 2011;23(3):233–40.

5. Miura Y, Ota S, Peterlin M et al. Subpopulation of synovial fibroblasts leads to osteochondrogenesis in a mouse model of chronic inflammatory rheumatoid arthritis. JBMR Plus 2018;3(6):1–10.

6. Mellado M, Martinz-Munoz L, Cascio G et al. T cell migration in rheumatoid arthritis. Front Immunol 2015;6:384.

7. Bustamante MF, Garcia-Carbonell R, Whisenant KD et al. Fibroblast-like synoviocyte metabolism in the pathogenesis of rheumatoid arthritis. Arthritis Res Ther 2017;19(110):1–12.

8. Xu L, Zhang Y, Wang Q et al. Bi-specific antibodies with high antigen-binding affinity identified by flow cytometry. Int Immunopharmacol 2015;24(2):463–73.

9. Byrne H, Conroy PJ, Whisstock JC et al. A tale of two specificities: bispecific antibodies for therapeutic and diagnostic applications. Trends Biotechnol 2013;31(11):621-32.

10. Taylor P, Kontermann RE. Dual targeting strategies with bispecific antibodies. mAbs 2012;4(2):182-97.

11. Spiess C, Zhai Q, Carter PJ. Alternative molecular formats and therapeutic applications for bispecific antibodies. Mol Immunol 2015;67(2):95–106.

12. Chon JH, Zarbis-Papastoitsis G. Advances in the production and downstream processing of antibodies. N Biotechnol 2011;28(5):458–63.

13. Klein C, Schaefer W, Regula JT et al. Engineering therapeutic bispecific antibodies using CrossMab technology. Methods 2019;154:21–31.

14. Michal P, Timo R, Wagne IL et al. FcRn: the architect behind the immune and non-immune functions of IgG and albumin. J Immunol 2015;194(10):4595–603.

15. Levin D, Golding B, Strome SE et al. Fc fusion as a platform technology: potential for modulating immunogenicity. Trends Biotechnol 2015;33(1):27–34.

16. Sedykh SE, Prinz VV, Buneva VN et al. Bispecific antibodies: design, therapy, perspectives. Drug Des Devel Ther 2018;12:195–208.

17. Xu T, Ying T, Wang L et al. A native-like bispecific antibody suppresses the inflammatory cytokine response by simultaneously neutralizing tumor necrosis factor-alpha and interleukin-17A. Oncotarget 2017;8(47):81860–72.

18. Noack M, Beringer A, Miossec P. Additive or synergistic interactions between IL-17A or IL-17F and TNF or IL-1β depend on the cell type. Front Immunol 2019;10:1–12.

19. Yoshitomi H. Regulation of immune responses and chronic inflammation by fibroblast-like synoviocytes. Front Immunol 2019;10:1–8.

20. Liu Z, Song L, Wang Y et al. A novel fusion protein attenuates

collagen – induced arthritis by targeting interleukin 17A and tumor necrosis factor α. Int J Pharm 2018;547(1– 2):72–82.
21. Fischer J, Hueber A, Wilson S et al. Combined inhibition of TNFα and IL-17 as therapeutic opportunity for treatment in rheumatoid arthritis: development and characterization of a novel bispecific antibody. Arthritis Rheumatol 2015;67(1):51–62.
22. Alzabin S, Abraham SM, Taher TE et al. Incomplete response of inflammatory arthritis to TNF-α blockade is associated with the Th17 pathway. Ann Rheum Dis 2012;71(10):1741–8.

LETTER TO THE EDITOR

Sevastiani Syrioti

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Dear editor,

In the ''Retrospective analysis of chronic myeloid leukemia patients in Trakya University School of Medicine," the authors summarize the use of imatinib which is a tyrosine kinase inhibitor (TKI) in chronic and accelerated phases of the disease as a first-line treatment (1). They stated that the side effects of drugs, insufficient responses, and non-compliances are reasons for switching the drug of choice. I read the article with great interest, paid special attention to the laboratory investigations and physical examinations, thus I would like to underline some points and suggest an alternative perspective to the clinical investigation and treatment options.

The laboratory results given in the study needed to have a clearly stated timeline based on the time of diagnosis. Likewise, some important parameters were missing such as uric acid, creatinine, potassium, phosphorus levels. The side effects that the patients and the clinicians face such as tumor lysis syndrome observed on newly diagnosed patients could be mentioned. Tumor lysis syndrome is a metabolic complication following rapid cancer therapy especially using chemotherapeutic drugs (2). It is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia which occur due to rapid lysis of tumor cells; leading to severe renal impairment. Therefore, the use of allopurinol in the presence of uric acid before starting TKIs is suggested (2). Malignant cells contain potassium, phosphorus and some purines. When these cells die spontaneously or secondary to therapy, the influx of intracellular substances into the extracellular fluid manifests the complications mentioned above.

Another treatment option is called leukapheresis procedure which is performed even in pregnant patients to avoid teratogenic effects of chemotherapy (3). There is plenty of evidence for the symptomatic improvement especially when it is used for patients with splenomegaly. Furthermore, the presence of pretreatment predictors like OCT-1 aid the prescription of TKIs. High levels of this protein indicate superior results and lower levels of the protein suggest a higher starting dose (4).

Finally, we have to consider the contribution of interferon-alpha as an alternative treatment in the first phases of myeloid leukemia instead of imatinib in combination with stem-cell transplantation since many trials of new drugs, new strategies, and combined therapies are being developed (5).

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REFERENCES

1. Akay FE, Koçyiğit B, Tan B et al. Retrospective analysis of chronic myeloid leukemia patients in Trakya university school of medicine. Turkish Med Stud J 2019;6(3):70-5.

2. Belay Y, Yirdaw K, Enawgaw B. Tumor lysis syndrome in patients with hematological malignancies. J Oncol 2017: 9684909.

3. Fitzgerald D, Rowe JM, Heal J. Leukapheresis for control of chronic myelogenous leukemia during pregnancy. Am J Hematol 1986;22(2):213-8.

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4. Thompson PA, Kantarjian HM, Cortes JE. Diagnosis and treatment of chronic myeloid leukemia in 2015. Mayo Clin Proc 2015;90(10):1440-54.

5. Baccarani M, Martinelli G, Rosti G et al. Imatinib and pegylated human recombinant interferon-alpha2b in early chronic-phase chronic myeloid leukemia. Blood 2004;104(13):4245-51.

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RETRACTIONS & ERRATA

Date: 2020, February

Errata

In the article by Özkan et al., entitled "Evaluating Orthorexia Tendency Among Trakya University Medical School Students" that was published in the January 2015 issue of Turkish Medical Student Journal, the name of an author was wrongly written. The Editorial Board reviewed the case and "Atila Ülkücü" is corrected as "Attila Ülkücü".

Authorship Contributions Form

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1. Authorship requires at least 3 contributions listed in the table below, including critical review of the manuscript, which is a mandatory contribution for all authors.
2. All authors are required to contribute to manuscript draft preparation, and critical review of its important intellectual content.
3. All authors are responsible for approval of the final proofs of the article
4. Those authors who do not fulfill the required number of contributions or do not meet criteria should be listed in the Acknowledgement section at the end of the manuscript.
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Contribution	Explanation	Contributing Authors
CONCEPT	The idea for research or article/hypothesis generation	
DESIGN	Planning the methods to generate hypothesis	
SUPERVISION	Supervision and responsibility for the organization and course of the project and the manuscript preparation	
RESOURCES	Supplying financial resources, equipment, space, and personnel vital to the project	
MATERIALS	Biological materials, reagents, referred patients	
DATA COLLECTION AND/OR PROCESSING	Responsibility for conducting experiments, management of patients, organizing and reporting data	
ANALYSIS AND/OR INTERPRETATION	Responsibility for presentation and logical explanation of results	
LITERATURE SEARCH	Responsibility for conducting literature search	
WRITING MANUSCRIPT	Responsibility for creation of an entire or the substantial part of the manuscript	
CRITICAL REVIEW	Reworking the final, before submission version of the manuscript for intellectual content, not just spelling and grammar check	
OTHER	For novel contributions:	

CORRESPONDING AUTHOR :

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2. The work under consideration for publication.
This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party—that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation, or commercial sponsor, check "Yes". Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. You should disclose interactions with ANY entity that could be considered broadly relevant to the work.
Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.
For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations, or academic institutions, need not be disclosed here (but can be acknowledged on the title page of the manuscript). For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships.
Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.
*If you are the corresponding author, and neither you nor your co-authors have any disclosures to declare under Sections 2, 3, or 4 below, you can check "Nothing to disclose" (see Section 1, line 7, page 2). In this case only, the disclosure applies to all authors, and the form is complete.

Section 1. Identifying Information
Complete by providing the requested information in the white boxes.

1. Given Name (First Name):		2. Surname Last Name):		3. Current Date:	
4. Are you the corresponding author?	___Yes	___No	If "No", name of corresponding author:		
5. Manuscript Title:					
6. Manuscript Identifying Number (if you know it):					
7. If you are the corresponding author, and neither you nor your co-authors have any disclosures to declare, check here:				___**Nothing to Disclose**	

Section 2. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

Complete each row by checking "No" or providing the requested information in the white boxes. Add rows as needed.

The Work Under Consideration for Publication

Type	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments
1. Grant					
2. Consulting fee or honorarium					
3. Support for travel to meetings for the study or other purposes					
4. Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like					
5. Payment for writing or reviewing the manuscript					
6. Provisions of writing assistance, medicines, equipment, or administrative support					
7. Other					

*This means money that your institution received for your efforts this study.

Section 3. Relevant financial activities outside the submitted work.

Please indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking "No" or providing the requested information in the white boxes.

Relevant Financial Activities Outside the Submitted Work

Type of Relationship (in alphabetical order)	No	Money Paid to You	Money to Your Institution*	Name of Entity	Comments
1. Board membership					
2. Consultancy					
3. Employment					
4. Expert testimony					
5. Grants/grants pending					
6. Payment for lectures including service on speakers bureaus					
7. Payment for manuscript preparation					
8. Patents (planned, pending or issued)					
9. Royalties					
10. Payment for development of educational presentations					
11. Stock/stock options					
12. Travel/accommodations/ meeting expenses unrelated to activities listed**					
13. Other (err on the side of full disclosure)					

*This means money that your institution received for your efforts.

**For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

Section 4. Other Relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

____No other relationships/conditions/circumstances that present a potential conflict of interest.

____Yes, the following relationships/conditions/circumstances are present (explain below):

At the time of manuscript acceptance, we ask that you update your disclosure statements if anything has changed. On occasion, we may ask you to disclose further information about reported relationships.

This form is adapted from the Author Disclosure Form created by the International Committee of Medical Journal Editors (ICMJE). The ICMJE has not endorsed nor approved the contents here. The official version of the ICMJE Author Disclosure Form is located at http://www.icmje.org/coi_disclosure.pdf

Acknowledgement of Authorship, Exclusive Publication Statement, Conflict of Interest Statement, and Transfer of Copyright Agreement

Authorship

All persons designated as authors should qualify for authorship. Each author should have participated sufficiently in the work to take public responsibility for the content.

Authorship credit should be based only on substantial contributions to 1) conception and design, or analysis and interpretation of data; and to 2) drafting the article or revising it critically for important intellectual content; and on 3) final approval of the version to be published. Conditions 1, 2, and 3 must all be met. Participation solely in the acquisition of funding or the collection of data does not justify authorship. General supervision of the research group is not sufficient for authorship. Any part of an article critical to its main conclusions must be the responsibility of at least one author. Editors may ask authors to describe what each contributed; this information may be published.

Increasingly, multicenter trials are attributed to a corporate author. All members of the group who are named as authors, either in the authorship position below the title or in a footnote, should fully meet the above criteria for authorship. Group members who do not meet these criteria should be listed, with their permission, in the Acknowledgments or in an appendix. The order of authorship should be a joint decision of the coauthors. Because the o ifferent ways, its meaning cannot be inferred accurately unless it is stated by the authors. Authors may wish to explain the order of authorship in a footnote.

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Conflict of interest for a given manuscript exists when a participant in the peer review and publication process-author, reviewer, and editor-has ties to activities that could inappropriately influence his or her judgment, whether or not judgment is in fact affected. Financial relationships with industry (for example, through employment, consultancies, stock ownership, honoraria, expert testimony), either directly or through immediate family, are usually considered to be the most important conflicts of interest. However, conflicts can occur for other reasons, such as personal relationships, academic competition, and intellectual passion.

Public trust in the peer review process and the credibility of published articles depend in part on how well conflict of interest is handled during writing, peer review, and editorial decision making. Bias can often be identified and eliminated by careful attention to the scientific methods and conclusions of the work. Financial relationships and their effects are less easily detected than other conflicts of interest. Participants in peer review and publication should disclose their conflicting interests, and the information should be made available so that others can judge their effects for themselves. Because readers may be less able to detect bias in review articles and editorials than in reports of original research, some journals do not accept reviews and editorials from authors with a conflict of interest.

When they submit a manuscript, whether an article or a letter, authors are responsible for recognizing and disclosing financial and other conflicts of interest that might bias their work. They should acknowledge in the manuscript all financial support for the work and other financial or personal connections to the work.

(*Reference: Uniform requirements for manuscripts submitted to biomedical journals. Ann Intern Med 1997;126:36-47)

Authors should clearly state below whether or not there are any conflicts of interest regarding the sub-mission and publication of the manuscript and its potential implications. .....

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Correspondent author:
Tel: Fax: GSM : e-mail:

CONSENT FORM for CASE REPORT

Title of Project:_____

1. I have read, and understood the Participant Information Sheet dated _____
2. I freely agree to the use of my medical records for the purpose of this study.
3. I understand that the case report will be published without my name attached and researchers will make every attempt to ensure my anonymity. I understand, however, that complete anonymity cannot be guaranteed.
4. I have been given a copy of the Participant Information Sheet and Consent Form to keep.

Name of Participant_____

Signature of Participant _____ Date _____

The participant was informed through phone call and a verbal consent was obtained.

The following section regarding the witness is not essential but may be appropriate for patients where the research teams feel that the participant should have a witness to the consent procedure.

Name of witness (if appropriate)_____

Signature of witness_____ Date _____

Name of Researcher_____

Signature of Researcher_____ Date_____

Name of Researcher

Signature of Researcher_____ Date_____