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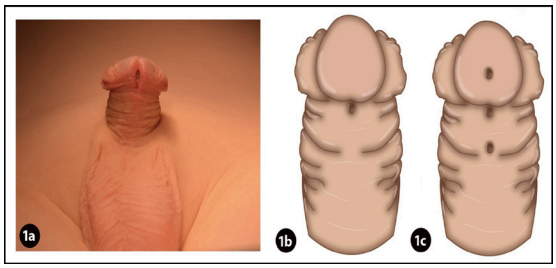

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Evaluation of colposcopy results for patients who are HPV DNA positive in KETEM

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ABSTRACT

We evaluated colposcopy and postoperative biopsy results in cases referred to our oncology center from the Cancer Early Diagnosis and Treatment Center (KETEM) due to Human Papilloma Virus (HPV) positivity and/or cervical premalignant lesion (CPL). A total of 1230 female patients who were admitted to Oncology outpatient clinic between January 2016 and December 2017 with positive HPV DNA screening tests from KETEM regardless of whether they had cervical premalignant lesion or not as a result of Papanicolaou smear (PAP smear) were included in the study. Colposcopy was performed in all cases and cervical biopsy was performed in patients who had suspicious lesions. No significant relationship was found between smoking status, educational status and financial status and HPV DNA screening test results ($p = 0.123$, $p = 0.201$, $p = 0.244$, respectively). The sensitivity of colposcopy to detect cervical premalignant lesions was 99.2% and positive predictive value (PPD) was 74.1%. In determining the cervical premalignant lesions, the sensitivity of smear was 41.3% and its specificity was 66.5%, PPV (positive predictive value) was 78.1% and NPV (negative predictive value) was 28.2%. In our study, the sensitivity of the HPV test to determine cervical premalignant lesions was 93.1%, PPV was 74%, specificity 86% and NPV was 30%. The accuracy of HPV types in determining CPLs was found to be (530 + 17)/776=71.4%. Positivity on the HPV DNA screening test is the leading risk factor for cervical cancer development. As a result, the first step in family medicine and KETEM activities is to reduce the frequency of these cancers and the complications related to the disease by increasing information and screening examination applications.

1. Introduction

Cervical cancer is the seventh among all cancers in the world, the second most common in cancer among women and third in cancer-induced deaths. According to research by Global Cancer Statistics 2012 published in 2015, 527,600 new cases of cervical cancer and 265,700 deaths were observed around the worldwide (Torre et al., 2015). Infections with oncogenic HPV types are thought to be involved in the etiopathogenesis of almost all cervical cancers and precancerous lesions, and HPV types 16 and 18 may be responsible for approximately 70% of all cervical cancers (Horry et

al., 2008). In addition, low education level, advanced age, obesity, active or passive smoking, early sexual intercourse, multiple sexual partners, multiparity, low socioeconomic status, and herpes simplex type 2 infection increase the frequency of cervical cancer (Munoz et al., 2002; Milutin et al., 2008).

Since the cervix is an easily accessible organ, early diagnosis and prognosis for cancers of this organ can be made with Pap smears. The Pap smear test was reported to reduce the incidence of cervical cancer by 79% and mortality by 70% since 1950. Especially in countries with organized screening programs, 60-70% decrease in the frequency and mortality of cervical cancer is reported (Türkiye Kanser İstatikleri, 2015). It can be used in screening of cervical cytology screening methods both in liquid based and conventional methods. In the past, colposcopy was mainly used to exclude asymptomatic early invasive cervical cancer, but is now used to diagnose preinvasive cervical disease (Cervical Cytology Screening, 2009). As a result, cytological, colposcopic and histological data are examined together to determine the right approach for the patient (Frank, 2008). Cytology and colposcopy do not compete with each other; on the contrary, they are complementary methods. Through colposcopy and subsequent biopsy, unnecessary conization and invasive surgical procedures have decreased. On the other hand, it is a personal procedure, highly dependent on the observer's assessment. Nowadays, because of the low sensitivity of cervical cytology, the approach in detecting the presence and type of HPV infection with cytology has come to the agenda. Today, it is emphasized that HPV should definitely exist for cervical cancer development and other risk factors increase the rate of virus exposure or viral persistence so it is important because it accelerates the carcinogenic process (Eroğlu et al., 2011). HPV is considered to be the etiologic agent in many cancers, especially anogenital and head and neck cancers. Nowadays, more than one HPV type has been detected and approximately 40 of them infect the anogenital area. Of these, 15 types (6, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82) are in the oncogenic high-risk group, 3 types (26, 53, 66) are in the low risk group, and 12 types (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81 and 89) are in the low risk group (Horry et al., 2008).

In the family medicine discipline, preventive medicine has an important place in addition to therapeutic health services. In terms of preventive medicine, cervical cancer screening methods are one of the few screening methods that reduce the incidence and mortality of invasive cancer and have proven effective in this respect. In order to identify women at risk, regular screening should be done between the ages of 30-65 at recommended intervals. The national standards for screening cervical cancer were determined by the Department of Cancer Control Center in the Ministry of Health and are implemented in Cancer Early Diagnosis and Treatment Centers (KETEM). Because of the high incidence of HPV DNA in all cervical cancers and precancerous lesions, detection of HPV DNA in addition to cervical smear screening programs for preinvasive lesions and HPV DNA typing are important (Munoz et al., 2002). The community-level cervical cancer screening program in Turkey (Pap smear and HPV DNA) began in 2014. In our study, we aimed to evaluate HPV DNA positive patients referred to our oncology center by family medicine and KETEM.

2. Material and method

In this study, we evaluated the colposcopic diagnosis and colposcopic biopsy results of 1230 cases who applied to the Oncology Outpatient Clinic of Tepecik Training and Research Hospital between January 2016 and December 2017 who were diagnosed with oncogenic HPV positive and/or had Pap smear results in KETEM and whose results were found to be pathological (ASCUS, ASC-H, LSIL, HSIL and AGC). The Local Ethics Committee approved the study. The universal principles of the Helsinki Declaration were implemented. Age, socioeconomic status, learning status, and smoking habits of the cases were recorded. Epidemiological data, cervical smear and HPV samples were taken and colposcopic examination and biopsies were performed in our oncology center. Epidemiological data, cervical smear and HPV samples were taken and colposcopic examination and biopsies were performed in our oncology center. In the etiopathogenesis of cervical cancer, HPV types 16, 18, 31, 33, 45, 51, 58, 59, and 68 are considered to be high risk, 53 and 66 are possibly high risk and 6, 11, 40, 54 and 70 are considered low risk (Milutin et al., 2008). The cases were divided into two groups as high and low risk groups. Those who were pregnant, had conization and hysterectomy operation, who had vaginal bleeding, bad obstetric history and suspected medical conditions were not included in the study. None of the patients had HPV vaccination.

All patients had colposcopic observations. None of the patients had HPV vaccination. All patients underwent colposcopic observations. Biopsy was performed for the patients whose colposcopic observation was evaluated to be problematic. Colposcopic examinations were performed with colloquial colposcopy device (colposcope 1D-21100, Leisegang GmbH, 2014-03, Germany) capable of 4.5 to 30 magnification with a green filter. The cervix was first screened at small magnification after washing with saline, and the green filter and vascularization pathologies were investigated. Then 3% acetic acid was applied and left for at least 60 seconds and then the cervix was re-scanned in small

and large magnifications. Lugol solution was applied afterwards to the location of the acetowhite areas and vascular pathologies were determined. After staining the cervix with Lugol solution, iodine-free areas were determined.

After staining the cervix with Lugol solution, iodine-free areas were determined. Acetowhite, mosaic, punctation, leukoplakia, and atypical veins were observed and biopsy was performed with cervical biopsy forceps. Patients with pathological colposcopic findings were treated at our center for treatment or advanced treatment procedures. The materials were sent to the pathology laboratory in formaldehyde. Cervical biopsy specimens were evaluated in the Pathology Unit.

Statistical method

Statistical analyses were performed using SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA) and R (Version 3.5.0) packages. Descriptive statistics are presented as mean ± standard deviation and median (min-max) for continuous variables and as number and percentage for categorical data.

The statistical distribution of the data was evaluated by Kolmogorov-Smirnov and Shapiro-Wilk tests. Homogeneity of variances was evaluated by the Levene test. According to HPV groups, non-parametric Kruskal Wallis test was used to compare the age of the patients. After Kruskal-Wallis test, post-hoc two-way comparison test was used in order to determine which groups caused the difference. Correlations between categorical variables and ratio comparisons were performed with Chi-square test or Fisher exact test. The correlation between smear 1 and smear 2 results was evaluated by McNemar Bowker test. Sensitivity, selectivity, positive predictive value, and negative predictive values were calculated for the evaluation of diagnosis according to the results of HPV DNA, pap smear and colposcopy biopsy. Statistical significance was accepted as $p < 0.05$.

3. Results

A total of 1230 patients with mean age of 43.12 ± 8.80 years for patients referred to our research center, were examined. The youngest patient was 20 years, while the oldest patient was 66 years old. HPV DNA test groups were significantly different in terms of age ($p = 0.004$). According to the post-hoc pairs comparison test results, there was no significant difference between patients in the low-middle and medium-high HPV DNA test groups (respectively, $p = 1.000$, $p = 0.557$). The age of the patients in the low and high HPV DNA test groups was significantly different ($p = 0.005$). The age group with high-risk HPV DNA test had lower median age (Fig.1). Age comparisons with HPV DNA test groups are given in Table 1. Of the cases, 435 (35.4%) had no education other than primary school, 690 (56.1%) were secondary school/high school graduates and 105 (8.5%) were university graduates. Only 129 (10.5%) of the cases had good socioeconomic status. In terms of smoking, 154 (12.5) of the patients smoked. No significant relationship was found between smoking status, educational status and financial status and HPV DNA screening test results ($p = 0.123$, $p = 0.201$, $p = 0.244$, respectively) (Table 2). The most common HPV types were HPV 16 in 546 (44.4%), and HPV 18 in 160 (13%). The frequency distribution of other HPV types in the low, middle and high-risk groups is shown in detail in the table. According to HPV types, the rate of those with high risk for cervical cancer was 86.7% (n = 1066), while 57 had moderate risk were (4.6%) and 8.7% had low risk (n = 107) (Table 3). As a result of the colposcopy procedure applied to patients included in the study, colposcopy of 464 patients (37%) was normal and colposcopy of 766 (63%) was evaluated as problematic. Of the 1230 patients, 766 patients underwent biopsy. The sensitivity of colposcopy in determining CPL was 99.2% and positive predictive value (PPV) was 74.1%. Considering colposcopy as a screening tool, the sensitivity for CPL was found to be high (99.2%), and unhealthy cervix (high/low grade lesion) was 99.2% sensitive to differentiation from healthy cervix (Table 4). In the cervical smear evaluation of 766 cervical biopsies; ASCUS was detected in 124 (16.2%), LSIL in 93 (12.1%), HSIL in 47 (6.1%), ASC-H in 26 (3.4%), and AGC in 11 (1.4%). When smear results were separated as normal and pathological, 301 cases were evaluated as pathological based on cervical biopsy results. According to Table 5, the sensitivity of pap smear for CPL was 41.3% and specificity was 66.5%, positive predictive value (PPV) was 78.1% and negative predictive value (NPV) was 28.2% (Table 5). Results of colposcopic biopsy revealed a total of 766 patients with HPV results, with 39 patients having low-risk HPV and 530 patients with moderate and high-risk HPV. In our study, the sensitivity of the HPV test for CPL determination was 93.1%, specificity 86%, PPV 74% and NPV 30%. The accuracy of HPV types in determining the cervical cell was found to be (530 + 17) /766=71.4% (Table 6).

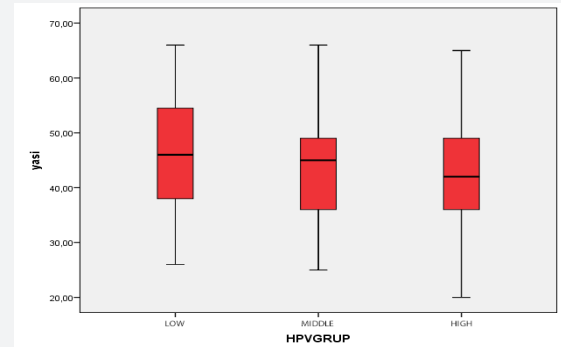

Fig. 1. Boxplot of the distribution of HPV levels according to the age of patients.

Table 1. Age comparisons according to HPV groups.

HPV Group	N	Mean ± SD	Median (min-max)	*p*	*p* value
Minimum (1)	107	45.77 ± 9.47	46 (26-66)		1-2: 1.000*
Average (2)	57	44.51 ± 9.59	45 (25-66)	**0.004***	**1-3: 0.005***
Maximum (3)	1066	42.78 ± 8.64	42 (20-65)		2-3: 0.557

* Kruskal Wallis test statistically significant (p<0.05)

Table 2. Demographic data and evaluation of HPV type.

			HPV			Total	p value
			Minimum	Average	Maximum		
School	**Primary school**	n	44	20	371	435	0.201
		%	10.1	4.6	85.3	100.0	
	Secondary school	n	56	36	598	690	
		%	8.1	5.2	86.7	100.0	
	University	n	7	1	97	105	
		%	6.7	1.0	92.4	100.0	
Wage	**Minimum Wage**	n	69	33	631	733	0.244
		%	9.4	4.5	86.1	100.0	
	Double Minimum Wage	n	28	22	318	368	
		%	7.6	6.0	86.4	100.0	
	Triple Minimum Wage	n	10	2	117	129	
		%	7.8	1.6	90.7	100.0	
Smoking habit	**Smoking**	n	7	6	141	154	0.123
		%	4.5	3.9	91.6	100.0	
	Non-smoking	n	100	51	925	1076	
		%	9.3	4.7	86.0	100.0	
Total		n	107	57	1066	1230	
		%	8.7	4.6	86.7	100.0	

* Chi-square test

Table 3. Distribution of HPV types.

HPV type	Frequency	Percent
16	546	44.4
18	160	13.0
31	28	2.3
33	15	1.2
35	31	2.5
36	1	0.1
38	1	0.1
39	36	2.9
41	3	0.2
42	14	1.1
43	1	0.1
45	12	1.0
46	5	0.4
49	6	0.5
51	61	5.0
52	37	3.0
53	24	2.0
54	13	1.1
55	6	0.5
56	49	4.0
58	39	3.2
59	33	2.7
60	1	0.1
61	16	1.3
62	7	0.6
66	33	2.7
68	18	1.5
69	4	0.3
70	17	1.4
76	1	0.1
81	8	0.7
82	2	0.2
84	2	0.2
Total	**1230**	**100**
Minimum	107	8.7
Average	57	4.6
Maximum	1066	86.7
Total	**1230**	**100**

Table 4. Evaluation of colposcopy.

			Biopsy		Total
			Normal	Pathologic	
Colposcopy	Normal results	n	0	4	4
	Problematic	n	197	565	762
Total		n	197	569	766

Sensitivity	0.992 (0.981-0.998)
Specificity	-
PPV	0.741 (0.709-0.772)
NPV	-

Table 5. Evaluation of smear.

Valid	**Normal Results**	507	66,8
	ascus	124	16,2
	lsıl	93	12,1
	asc-h	26	3,4
	hsıl	47	6,1
	agc	11	1,4
	Total	766	100,0

Comparison of smear and biopsy:

			Biopsy		Total
			Normal	Pathological	
smear1	Normal	Count	131	334	465
	Pathological	Count	66	235	301
Total		Count	197	569	766

Sensitivity	0.413 (0.372-0.455)
Specificity	0.665 (0.594-0.730)
PPV	0.781 (0.729-0.825)
NPV	0.282 (0.242-0.325)

Table 6. Comparison of HPV biopsy.

			Biopsy		Total
			Normal	Pathological	
HPV	Normal	n	17	39	56
	Pathological	n	180	530	710
Total		n	197	569	766

Sensitivity	0.931 (0.907-0.950)
Specificity	0.086 (0.053-0.137)
PPV	0.746 (0.712-0.778)
NPV	0.304 (0.192-0.443)

4. Discussion

KETEM employees and family medicine centers are the most common ways to be correctly informed about the importance of positive cervical smear by pap Smear test screening in our country. In this way, more effective results are obtained for cancer prevention, early diagnosis and treatment methods. In addition, the provision of Pap Smear and oncogenic HPV DNA typing by the state and targeting this service to reach the whole community will positively affect service delivery and healthy community development. For this purpose, our primary aim should be to ensure that all women are properly informed about cervical cancer and pap smear screening at KETEM and family medicine centers. In recent years, many studies have been completed in Turkey and around the world to evaluate the information including cervical cancer risk factors, clinical findings, early diagnosis and prevention methods of cervical cancer, and to increase awareness. In many studies on this subject, it is known that health practitioners working in KETEM and family medicine centers are well aware of their knowledge about the subject and they are sensitive to the patients who apply for these or other reasons (Dönmez, 2007; Can et al., 2010). As seen in many studies, the application of pap smear screening tests in our country and developing countries, unlike developed countries, was found to be extremely inadequate. Paradoxically, in our country, sociocultural level and level of knowledge about cervical cancer was found to be much lower than expected. This may be due to monogamy, ignorance, value judgments and avoidance of examination (Dönmez, 2007; Can et al., 2010).

HPV infection is the most common infectious disease among sexually transmitted infections. HPV has more than forty types which lead to genital tract infections. Approximately 90% of these infections are asymptomatic and spontaneously regress within two years. However, recurrent infections due to some HPV types can lead to cervical cancer and genital warts. HPV types 16 and 18 are associated with approximately 70% of cervical cancers worldwide; HPV types 6, 11, 16, 18 are related to 90% of cases of genital warts (Milutin et al., 2008). Studies conducted in Turkey show that the prevalence of HPV infection in women ranges from 2% to 20% (Akhan, 2007). In addition, the most common type, with or without cytological abnormalities, is HPV type 16. Cervical cancer is the tenth most common cancer among women in our country (T. C. Sağlık Bakanlığı Sağlık İstatistikleri Yıllığı, 2015). There are about 2000 new cases of cervical cancer in our country every year. Although the prevalence of HPV infection and cervical cancer is considered to be lower in Turkey than in the world, some studies have found that the prevalence of HPV infection in women has similar to rates to the rest of the world (Akhan, 2007). This shows us that cervical cancer is going to become one of the prominent cancers in addition to others. Vaccination is the most effective method of preventing HPV infection and related diseases. This suggests that it is not enough to increase the family physician's knowledge or increase vaccination rates in order to achieve a certain level of cervical cancer prevention. It also points out the need to focus on other methods.

High rates of HPV DNA are found in cervical cancer patients. Especially HPV 16 and 18 positivity were higher than 70%. Of women, 50-80% experience HPV infection at least once in their lifetime; 50% of these are oncogenic HPV types (Munoz et al., 2003). Many HPV infections are eliminated by the immune system with 70% in 1 year and 90% in 2 years. Especially if the infection caused by high-risk HPV types (types 16 and 18) does not improve, it takes 15-20 years to develop cervical cancer. Therefore, in order to determine people at risk and to perform the appropriate clinical follow-up, cervical smear is widely used, in addition to the detection and typing of HPV infection (Munoz et al., 2003). For this purpose, various methods were developed for the identification and types of HPV infection.

The most well-known HPV types associated with cervical cancer and cancer precursor lesions are HPV 16 and 18, and less frequently HPV 31, 33, 45, 52, 58, and 59. Interregional changes are observed in the frequency of types other than the most common HPV 16 and 18 in the world (Dönmez, 2007). In our study, when HPV 16 and 18 were combined together, those infected with these viruses accounted for 57% of our study patients. In our country, there are few studies which include both cytological abnormality and frequency of HPV infection. We planned our work in this direction to emphasize the importance of other HPV types. In our study, the relationship between age, smoking, economic status and HPV was evaluated. There was a significant relationship between age and HPV oncogenic high type, but no relationship was found with the other factors. There was no statistically significant relationship between HPV DNA positivity and age in the study by Özçelik et al. (2003). In our study, the risk factors for cervical cancer were consistent with most studies in the literature. A statistically significant relationship was found between age and HPV infection.

In a study of 53 patients presenting with the complaint of genital discharge and having cervical erosion by Aktepe et al. (2007), HPV positivity was reported in 1 (1.8%) case who had cytologically detected HSIL in cervical smear. In the study by Ergünay et al. (2007), HPV positivity was found in 80% of cases with pathologic cervical smear and HPV 16 in 50% of HPV types, HPV 18 in 10.7%, and HPV 53 in 7.1%. In the study by Sapmaz et al. (2003), HPV positivity was 38% (33% HPV 16 and 5% HPV 18) in cervical intraepithelial neoplasia (CIN) and 7.5% in the control group (5% HPV 16 and 2.5% HPV 18) respectively. In our study, the prevalence of high oncogenic HPV was 86.7% (Table 3). The reason for this may be the fact that it is a tertiary care center in the region and the oncology clinic is offered as a separate

service from other branches. In our study, the prevalence of high oncogenic HPV was 86.7% (Table 3). Another reason for the high oncogenic risk HPV positivity may be the fact that the study was performed in cases with risk for cervical cancer and HPV. The most common types of HPV infections were 44.4% HPV 16 and 13% HPV 18, then HPV 31, 33.35, 39, 45, 51, 52, 56, 58, 59, 68, and 82 (Table 3). In our study, in addition to the most common HPV types, other high-risk types of HPV are different from other studies. Since other rare HPV types may cause cervical cancer, these patients should also be referred to a gynecological oncology center without delay and should be directed to biopsy if necessary.

The slow natural course of cervical cancer reveals the importance of screening programs for the early recognition of dysplastic lesions and prevention of progression to invasive cancer. Many clinicians support the combination of cytology and colposcopy in primary screening, hoping to reduce false negative results. Colposcopy is an easily applicable method that requires education and determines cancer lesions (Kyrgiou et al., 2006). In our study, colposcopy was used as a secondary screening tool to confirm the cases diagnosed as pathological on pap smear. In a meta-analysis, the sensitivity was found to be between 87-99% (Mitchell et al., 1998). Similar sensitivities were reported in many other studies. On the other hand, as a colposcopy screening tool, high sensitivity and negative predictive value were calculated as 74% and 99%, respectively. In a recent study of 1850 patients, the sensitivity of colposcopy as diagnostic procedure was 52-98% and specificity was 45-87%. The effect of the number of colposcopic biopsies on the biopsy sensitivity was first examined by Gage and was 68.3% when one biopsy was performed, 81.8% when two biopsies were performed, and 83.3% when three biopsies were performed. In the study performed by Pretorius, the sensitivity was found to be 52.6% for 0-2 biopsy and 85.2% for 3 to 4 biopsies (Pretorius et al., 2006). A large number of biopsies from different quadrants (3 or 4) are associated with high sensitivity. In our study, sensitivity of the study group to high HPV type cases may be high (Table 4) due the fact that biopsy was obtained from at least four quadrants, and the study group contained more high-risk HPV type.

In 301 cases with cytological abnormalities in cervical smear samples, HPV positivity was found to be 37.46%. Although the rates were different in our study, the most common types were HPV 16 and 18 in accordance with other studies in our country. The difference in both HPV positivity and type distribution in studies can be attributed to the sample population, age, examination area, application complaint, and presence of non-homogeneous cases such as presence of risk factors for cervical cancer and different techniques used. The cervical cytological abnormality rate was found to be 1.2% in a cervical vaginal cytology study performed by Ergeneli et al. (2001). In a study of 4122 cases by Bozkurt et al. (2007), cervical cytologic abnormality rate was found to be 4.3%. In a study which evaluated 6706 cervico-vaginal smears by Özdamar et al. (2006) cytological abnormality rate was evaluated as 1.5%. In our study, 33.2% of the epithelial cell abnormalities in cervical smear may be due to the fact that the sampled group consists of few and risky cases (Table 5). According to Wright et al., high-risk HPV DNA positivity is 74-88% for ASC-H and 76.6% for LSIL. High HPV (+) in ASC-H, HSIL, and LSIL lesions decreases the diagnostic value of HPV test in these cytological results. Colposcopy should be the first attempt at diagnosis for these lesions (Thomas et al., 2007). In our study, 124 ASCUS and 93 LSIL cases were detected in 766 patients who underwent biopsy. A number of factors should be considered in the management of women diagnosed with ASC-H. The prevalence of HSIL was higher in women with ASC-H compared to ASCUS. Although the prevalence of CIN II-III in women with ASC in the USA is 7-12%, the prevalence of CIN II-III in ASC-H is 26-68%. These rates reflect the importance of the diagnosis of ASC-H. Of the biopsy patients, 26 (3.4%) were HPC-DNA positive and had ASC-H. As a result, ASC-H should be evaluated as equivalent to HSIL and should be followed closely (Ergunay et al., 2007). Patients who attend with suspicious smears should be given importance even if the severity of the lesion is relatively low (Thomas et al., 2007). In our results, the sensitivity of the smear for diagnosis of cervical pathologies was 66%, and this test was found to be indispensable in cancer screening for women in the practice of family medicine and gynecology oncology.

When the population is screened, approximately 10% of women have minor cytological abnormalities (such as ASCUS, LSIL) in their cervical smears (Wright et al., 2002). Many authors suggested monitoring these cytological abnormalities, postponed referral, and thought that spontaneous regression would be a treatment option. In this case, there may be a hidden high-grade lesion, but this may be masked as a low-grade cytologic phenotype or may occur during screening intervals, in which case monitoring policies may compromise some women in terms of invasive disease development (Kyrgiou et al., 2006). According to the evidence that we found, in 5-47% of lesions with low-grade phenotype, histologically high-grade lesion was revealed in reality. One of the management options is to carry out colposcopy urgently in order to distinguish all women who have minor cytological findings or those with high-risk disease. Accordingly, patients should be immediately referred to colposcopy after a low-grade smear result (Kyrgiou et al., 2006).

HPV testing allows rapid diagnosis in cervical premalignant event detection. It is known that there was increased risk of high-grade lesions, low-grade lesions and carcinoma in HPV (+) cases. In another study, the CIN2/3 ratio in HPV (+) was reported as 15-27% and

in HPV (-) the same ratio was less than 2% (Arbyn et al., 2005). In addition to the 100% negative predictive value of the HPV DNA screening test, continuous smear control, colposcopy and biopsy ensure that patients can safely avoid this condition (Syrjanen and Syrjanen, 1999). In many studies, researchers have found the HPV DNA screening test to be more sensitive than PAP smears in determining PML (Schneider et al., 2000). In another study that included 46009 women, the sensitivity of HPV DNA for PML was stated as 89.2% and the sensitivity of PAP smear was 76.2% (Manos et al., 1999). In the ALTS group study which was conducted in 2003, Guido et al. (2003) examined 1539 patients who had oncogenically risky HPV infection.

In conclusion, women who are at risk of cervical cancer should be closely monitored and precautions should be taken for women with cervical cancer due to high positivity especially with oncogenic HPV types. In fact, the greatest risk for cervical cancer is not having any pap-smear and HPV type assessment, or not recurring at the required frequency. Colposcopy-guided biopsy is the gold standard for the diagnosis of cervical premalignant lesions. Cytological, colposcopic and histological data should be examined together and the right approach should be provided for the patient.

REFERENCES

Akhan, S.E., 2007. Ülkemizde servikal kanser epidemiyolojisi ve HPV serotipleri. ANKEM Derg. 21, 96-98.

Aktepe, O., Altındiş, M., Aktepe, F., Yılmazer, M., Fenkçi, V., 2007. Risk altındaki kadınların servikal örneklerinde human papilloma virus araştırılması. Osmangazi J. Med. 29, 131–135.

Arbyn, M., Paraskevaidis, E., Martin-Hirsch, P., Prendiville, W., Dillner, J, 2005. Clinical utility of HPV-DNA detection: Triage of minor cervical lesions, follow-up of women treated for high-grade CIN: an update of pooled evidence. Gynecol. Oncol. 99, 7-11.

Bozkurt, T.T., 2007. 2000-2005 yılları arasında İstanbul Eğitim ve Araştırma Hastanesi servikal smear tarama sonuçlarımız. Uzmanlık Tezi. İstanbul: Sağlık Bakanlığı İstanbul Eğitim ve Araştırma Hastanesi, Aile Hekimliği Bölümü.

Can, H., Öztürk, Y.K., Güçlü, Y.A., Öztürk, F., Demir, Ş., 2010. Kadın Sağlık Çalışanlarının Serviks Kanseri Farkındalığı. Tepecik Eğit. Hast. Derg. 20, 77-84.

Cervical Cytology Screening. 2009. ACOG Practice Bulletin No 109. ACOG. 114, 1409-1420.

Dönmez, A.G., 2007. Şişli Etfal Eğitim ve Araştırma Hastanesi'nde çalışan kadın sağlık personelinin serviks kanserine ilişkin bilgi düzeyinin ve farkındalığının araştırılması. Tıpta uzmanlık tezi. S.B. Şişli Etfal Eğitim ve Araştırma Hastanesi, Aile Hekimliği Kliniği, İstanbul.

Ergeneli, M.H., Duran, E.H., Ergin, T., Demirhan, B., Erdogan, M., 2001. Atypical squamous cells of undetermined significance. Clinical experience in a Turkish university hospital. Eur. J. Obstet. Gynecol. Reprod. Biol. 96, 108-110.

Ergünay, K., Mısırlıoglu, M., Fırat, P., 2007. Sitolojik olarak anomali saptanan serviks örneklerinde insan papilloma virus DNA'sının araştırılması ve virusun tiplendirilmesi. Mikrobiyol. Bült. 41, 219-226.

Eroğlu, C., Keşli, R., Eryılmaz, M.A., Ünlü, Y., Gönenç, O., Çelik, Ç., 2011. Serviks kanseri için riski olan kadınlarda HPV tiplendirmesi ve HPV sıklığının risk faktörleri ve servikal smearle ilişkisi. Nobel Med. 7, 72–77.

Frank, J. E., 2008. The Colposcopic Examination. J. Midwifery Womens Health. 53, 447-452.

Guido, R., Schiffman, M., Solomon, D., 2003. ASCUS LSIL Triage Study (ALTS) Group. Postcolposcopy management strategies for women referred with low-grade squamous intraepithelial lesions or human papillomavirus DNA-positive atypical squamous cells of undetermined significance: a two-year prospective study. Am. J. Obstet. Gynecol. 188, 1401-1405.

Hoory, T., Monie, A., Gravitt, P., Wu, T.C., 2008. Molecular epidemiology of human papillomavirus. J. Formos. Med. Assoc. 107, 198-217.

Kyrgiou, M., Tsoumpou, I., Vrekoussis, T., 2006. The up-to-date evidence on colposcopy practice and treatment of cervical intraepithelial neoplasia: The cochrane colposcopy &cervical cytopathology collaborative group (C5 group) approach. Cancer Treat. Rev. 32, 516-523.

Manos, M.M., Kinney, W.K., Hurley, L.B., 1999. Identifying women with cervical neoplasia: using human papillomavirus DNA testing for equivocal Papanicolaou results. KAISER study. JAMA. 281, 1605-1610.

Milutin, G.N., Sabol, I., Matovina, M., Spaventi, S., Grce, M., 2008. Detection and typing of human papillomaviruses combining different methods: polymerase chain reaction, restriction fragment length polymorphism, line probe assay and sequencing. Pathol. Oncol. Res. 14(4), 355-363.

Mitchell, M.F., Schottenfeld, D., Tortolero-Luna, G., Cantor, S.B., Richards-Kortum, R., 1998. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. Obstet. Gynecol. 91, 626-631.

Munoz, N., Bosch, F.X., de Sanjose, S., 2003. Epidemiologic classification of human papillomavirus types associated with cervical cancer. N. Eng. J. Med. 348, 518-527.

Munoz, N., Franceschi, S., Bosetti, C., Moreno, V., Herrero, R., Smith, J.S., 2002. Role of parity and human papillomavirus in cervical cancer: the IARC multicentric case-control study. Lancet. 359, 1093-1101.

Özcelik, B., Serin, I.S., Gökahmetoğlu, S., Başbuğ, M., Erez, R., 2003. Human papillomavirus frequency of women at low risk of developing cervical cancer: a preliminary study from a Turkish University. Eur. J. Gynaecol. Oncol. 24, 157-159.

Özdamar, Ş.O., Bektaş, S., Barut, F., 2006. Zonguldak Karaelmas Üniversitesi Tıp Fakültesi Hastanesi'nin 2003-2005 yılları sitoloji deneyimi. Türk Patoloji Derg. 22, 92-95.

Pretorius, R.G., Peterson, P., Azizi, F., 2006. Subsequent risk and presentation of cervical intraepithelial neoplasia (CIN) 3 or cancer after a colposcopic diagnosis of CIN 1 or less. Am. J. Obstet. Gynecol. 195, 1260-1265.

Sapmaz, E., Şimşek, M., Çelik, H., Kumru, S., Doymaz, M.Z., 2003. Bölgemizdeki servikal intraepitelyal neoplazi vakalarında HPV 16 ve 18 genomlarının PCR yöntemi ile araştırılması. Türkiye Klinikleri J. Gynecol. Obst. 13, 58-61.

Schneider, A., Hoyer, H., Lotz, B., 2000. Screening for high-grade cervical intra-epithelial neoplasia and cancer by testing for high-risk HPV, routine cytology or colposcopy. Int. J. Cancer. 89, 529-534.

Syrjanen, S.M., Syrjanen, K.J., 1999. New concepts on the role of human papillomavirus in cell cycle regulation. Ann. Med. 31, 175–187.

T. C. Sağlık Bakanlığı Sağlık İstatistikleri Yıllığı. 2015. Yayın No:1054. Ankara: Sistem Ofset Basım Yayın. 36–37.

Wright, T.C.Jr., Massad, L.S., Dunton, C.J., Spitzer, M., Wilkinson, E.J., Solomon, D., 2007. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. J. Low. Genit. Tract. Dis. 11, 201-222.

Torre, L.A., Bray, F., Siegel, R.L., Ferlay, J., Lortet-TieulentJemal, A., 2015. Global cancer statistics, 2012. CA-Cancer J. Clin. 65, 87-108.

Türkiye Kanser İstatistikleri, 2015. http://www.kanser.gov.tr/ Dosya/ca_istatistik/ANA_rapor_2012 sooonn.pdf (Erişim tarihi:25.12.2015).

Wright, T.C., Cox, J.T., Massad, L.S., Wilkinson, E.J., 2002. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. JAMA. 287, 2120-2129.

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Clinical Research

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Experiences on the primary distal hypospadias surgery

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ABSTRACT

The aim of this study is to contribute to a better understanding and treatment of hypospadias by a surgical technique. We applied a surgical technique for primary distal hypospadias, 118 cases in our clinic between 2007 and 2017. The surgical technique for the hypospadias: the first step is that extending the urethra from the proximal to the distal by means of glandular incision, the second step is to make an incision line under the glans and last one is giving an cosmetic appearance to penis. Glandular opening developed in two (1.6%) of these cases, and urethral fistula in four (3.2%). One of the cases of urethral fistula was accompanied by meatal stenosis; in addition, meatal stenosis was developed in a total of five cases and external meatotomy was performed in one of these. The other four cases were corrected with urethral dilation. The technique we apply is quite simple; and can easily be applied in the treatment of all forms of distal hypospadias. It is suggested that it represents a significant therapeutic option in distal hypospadias surgery since, in addition to being easy to perform; it also has low complication rates and provides satisfactory cosmetic and functional outcomes. It is well known that complication rates are declining significantly with advances in existing surgical techniques. We believe that further development is required in hypospadias surgery to get better results. Applied technique in our clinic might be a surgical option in terms of cosmetic appearance and general complications.

1. Introduction

Hypospadias is the second most common anomaly in males after undescended testis (1/300) (Bouty et al., 2015). Hypospadias is a condition in which the opening of the urethra appears anywhere along the ventral region of the penis due to penile structures failing to close fully during embryogenesis (Van der Horst and de Wall, 2017). Hypospadias is classified depending on the preoperative level of the meatus. Glandular, coronal and distal penile cases are known as distal hypospadias, while mid-penile, proximal penile, penoscrotal and perineal cases are known as proximal hypospadias (Duckett, 1989; Bouty et al., 2015). Seventy percent of all hypospadias are distal, and 30% are proximal (Duckett, 1989; Riedmiller et al., 2001). Surgical treatment of hypospadias is generally recommended between six and 18 months of age. This study discusses an approach for the surgical treatment of distal hypospadias. Although many different methods have been appliedup to this date in the surgical treatment of hypospadias, no perfect method has yet been identified (Keays and Dave, 2017). Hypospadias surgery has undergone a major evolution, but the aim of surgery has

remained unchanged. This is to achieve a functional and cosmetically acceptable penis in a single session. The aim of successful hypospadias repair is to achieve a vertical, cleft-type glandular meatus, a conical glans, a penis that remains straight in an erectile state, and a smooth and healthy skin.

The aim of this study is to review the performance, results, and complications of the method applied in the clinic for the repairing of distal hypospadias.

2. Material and methods

We applied a surgical technique in 118 cases in 2007-2017. All cases were distal hypospadias, and were treated by the same surgeon (Fig. 1). General anesthesia was performed in all cases. First, an incision of sufficient depth to install a urethral catheter as far as the opening of the original meatus was opened from the apex of the glans (Fig. 2). This incision was subsequently sutured with 4/0 polyglactin such as to connect it to the glans with a meatal ring (Fig. 2). This suture was left long for subsequent ureteric stent fixation. Following suturing, the openings remaining on either side of the glans were sutured. We used 8 or 10 F urethral catheters, depending on the width of the urethra. A flap was prepared using the flip-flap technique to close the ventral opening (Fig. 2). The circumcision line was completed as far as the dorsal aspect, and the penile skin was degloved (Fig. 3). Parallel longitudinal incisions extending from the meatus to the distal aspect were made in order to constitute the posterior wall of the urethra (Fig. 3). The glandular wings were dissected as laterally as possible for easier closure of the glans. The flap was then reversed and sutured distally with 6/0 polyglactin and audrethral tube was established with the attachment of suture to the openings on the sides (Fig. 3). A sling suture was placed on the extreme tip of the flap to create an external meatus. Subcutaneous support sutures were first used to close the glans, followed by a matrix suture with 4/0 polyglactin (Fig. 3). An external meatus was established with the help of the sutures applied to the tip of the flap. The circumcision line was closed with 5/0 polyglactin (Fig. 4). The penis was then wrapped in a moderately tight Copan self-adherent wrap. The urethral catheter was fixed by plaster to the adnominal wall to avoid pressure on the suture line.

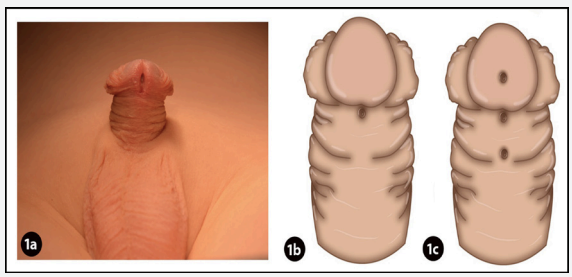

Fig. 1. 1a, 1b, 1c; all the patients to whom we applied our technique had distal hypospadias.

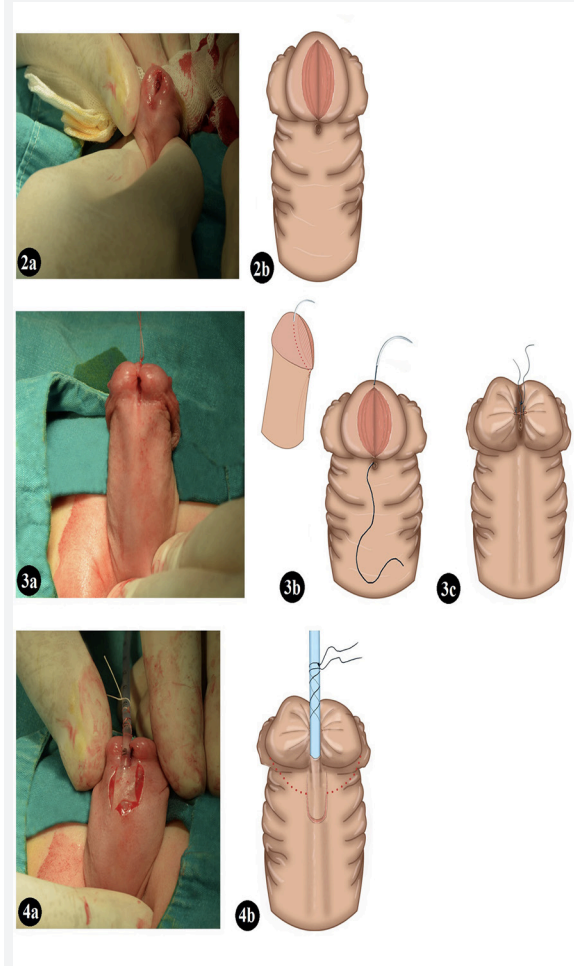

Fig. 2. 2a, 2b; an incision with a depth that allows the placement of the urethral catheter was made from the glans apex to the location of opening of the original mea. 3a, 3b,3c; the incision was sutured to join the mea ring with the glans apex. 4a, 4b; the flap was prepared with the flip-flap technique to close the ventral opening.

Broad-spectrum intravenous antibiotics were started 1 h before surgery and were maintained a day postoperatively. Oral antibiotics were used until removal of the catheter on the third day. Dressings were opened on the third day if no postoperative bleeding and wetting was present. The urethral catheter was removed on day 10. Urine cultures were performed preoperatively and between five days and one month postoperatively. Patient satisfaction, penile appearance, type of urination, meatal stenosis, urethral stenosis, urethrocutaneous fistula and penile deformity were assessed during a period of one-month, if anyone has a complication this period was extended. This retrospective study was conducted in accordance with the ethical principles defined in the Helsinki Declaration.

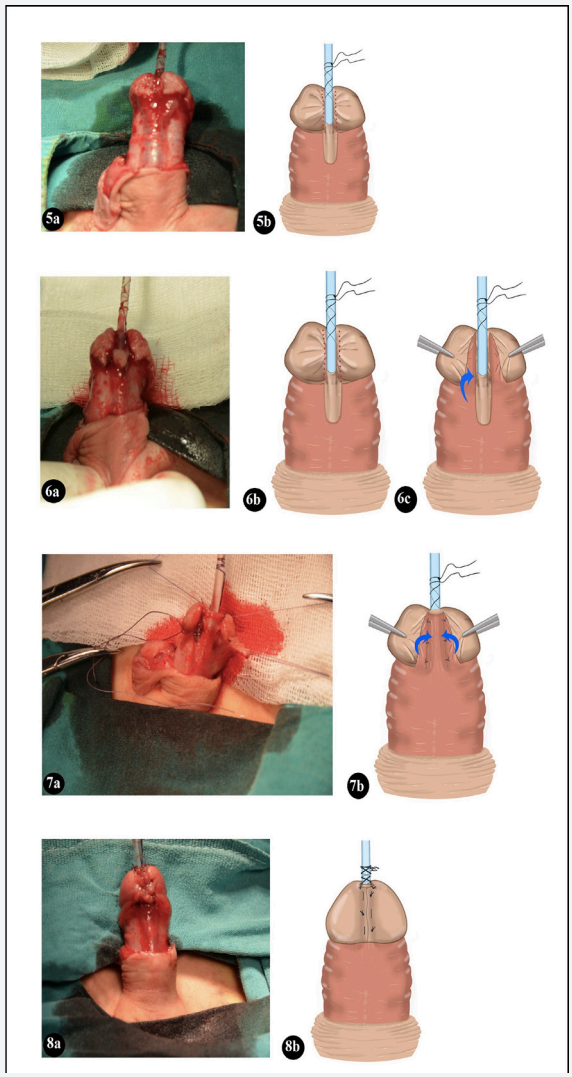

Fig. 3. 5a, 5b; the circumcision line was completed and the penis was degloved. 6a, 6b, 6c; parallel longitudinal incisions were made extending to distal from the mea to form theurethra posterior wall. 7a, 7b; the flap was inverted to form a urethral tube and theglandular wings were dissected as far as possible to the lateral. 8a, 8b; glans wasclosed in the form of a mattress suture after subcutaneous support sutures wereinserted.

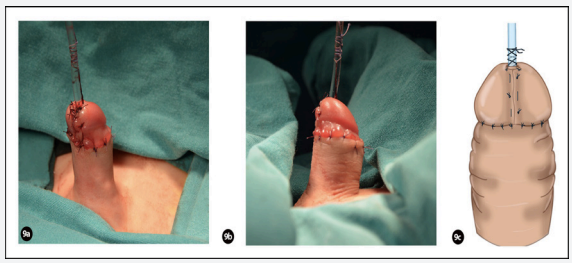

Fig. 4. 9a, 9b, 9c; the circumcision line was closed.

Statistical analysis

No statistical analysis was performed.

3. Results

One hundred eighteen cases were included in the study. Mean age at surgery was 6.08 years. The youngest patient was aged 10 months and the oldest 16 years. External meatal location was coronal in 27 cases, subcoronal in 52 and mid-penile in 39. Cases with advanced penile curvature were excluded. If no curvature was observed at erection tests following careful removal by dissection of the bands causing the curvature, such patients were included.

Mean duration of stent placement was 8 days (min 6, max 12 days), and mean length of hospital stay was five days (min. 3, max. 13 days). Two cases (1.6%) in the total were opened completely due to infection. Urethral fistula developed in four (3.2%) cases. Meatal stenosis was also not present in one of these cases but also occurred in five other cases. The patients in which opening was seen due to infection were aged eight and 14 years. These cases were subsequently corrected with secondary hypospadias repair. As usual re-operation was required in the fistula cases. External meatotomy was performed in one case of meatal stenosis. The others were treated with dilatation. Postoperative cosmetic appearances satisfactory to the family and the physician were achieved in all cases. Cases were followed-up for between one month and three years postoperatively.

4. Discussion

The earliest appropriate age for repair in cases of hypospadias is regarded as between eight and 18 months (Weber et al., 2009; Bush et al., 2013). However, in their retrospective study, Weber et al. reported that there is no ideal age affecting the success of hypospadias repair (Bush et al., 2015). The reason why the majority of cases of digital hypospadias in our clinic are aged over two years is that cases were not diagnosed in the newborn period or that physicians possessed incorrect information concerning the ideal operative age. Patients generally coming from rural areas in our region were noticeably older. Two cases with complete glans opening in our series were significantly older in comparison of the mean age of hypospadias surgery in the world. There are also studies suggesting that hypospadias repair is difficult at early ages when penises are so small, and that complication rates are high (Snodgrass et al., 2010; da Silva et al., 2014). No complications occurred in any of our cases performed under 18 months.

Various techniques have been used for many years in the treatment of distal hypospadias. In the light of the wide diversity of treatments, it appears that the search is still continuing, that there is no consensus on one correct method and that the field is still open to further developments. The currently most frequently employed

techniques are the meatoplasty and glanduloplasty (MAGPI), Mathieu and tubularized incised plate (TIPU) methods. Hypospadias surgery requires a specific experience because of the possibility of complications. Surgeons performing hypospadias surgery therefore wish to employ the method involving the fewest complications and the best cosmetic and functional outcomes. At the same time, it is important for the technique to be easy to perform. Several novel surgical techniques have been described for lower complication rates and a better cosmetic appearance (Snodgrass et al., 2010; Warren and Nicol, 2016). Despite the development of these novel techniques, complications may still be observed following hypospadias surgery at between 6% and 30%, depending on the severity of the anomaly (Park et al., 1994; Snodgrass, 1994). Complication rates of between 1.2% and 6% have been reported by even the best surgeons with the MAGPI technique (Park et al., 1994). An operative time of 115 min and a complication rate of 14.8% have been reported for the Mathieu technique. There are also complaints of a poor meatal cosmetic appearance (Snodgrass, 1994; Wilkinson et al., 2012; Hueber et al., 2015; Pfistermuller et al., 2015). A complication rate of 7% and a mean operative time of 75 min have been reported in even the best centers with the TIPU method. Severe problems are also encountered in cases with curvature with this technique (Snodgrass, 1994). Operative time in our clinic using the described technique is approximately 45 min.

We observed lower complication rates with the technique we have applied in our clinic compared to all these other three methods. We noted three basic problems that can give rise to complications in all the techniques. The first is a smaller suture line steam in order to prevent fistula development. The second is to create a comfortable urethra and external meatus causing urethral and meatal stenosis, and the third is to achieve a conical glans.

The main benefit of the presented technique reduces the suture line steam, for this aim we placed the suture that is applied to the incision from the apex of the glans to the original meatus. Very few sutures were then applied to the lateral aspect of the reversed flap. These sutures generally remained beneath the glans when this was closed. On the other hand, there are many different surgical techniques have been used for the treatment of hypospadias, as seen in the previously used surgical techniques (Elganainy et al., 2010; Wilkinson et al., 2012; Pfistermuller et al., 2015). But they have left long suture line steam on the penis in comparison of the presented technique. This means a high complication rate after surgery would be seen in the used surgical approaches. One of the most important points for surgeons is an efficient surgery involving few number of sutures, short suture line steam and one of the best clinical outcomes after surgery. This surgeon who is an expert on it has done a long period of hypospadias surgeries in our hospital, we did not see any serious surgical complication in comparison of the previous (Park et al., 1994; Elganainy et al., 2010; Wilkinson et al., 2012; Warren and Nicol, 2016). Some of the complications in our cases are given. The risk of fistula developing in case of a severe infection was quite low, if the glans was not opened (3.2%). Glans opening occurred in only two cases in our series (1.6%). These patients were aged eight and 14 years. It was attributed to genital secretions, infection, and nocturnal erection. On the other hand, we showed that the erections do have an adverse impact on our technique even in the adult age group. Since we treated these two cases of opening using the same technique in the second surgery of hypospadias. We also observed the applicability of this technique in circumcised cases and no such opening occurred in younger patients.

The glandular wings were dissected as laterally as possible in order not to compress the urethral stent so as to prevent urethral narrowing and meatal stenosis. Particular care was taken in closing the glans to ensure that the stent could move freely. Finally, the tip of the flap was used in establishing an external meatus appropriate to the original. Care was taken that meatal integrity had formed when we removed the urethral stent. Ibuprofen was administered for analgesia during the time the stent was in place. The urethral stent was normally left in place for 10 days and fixed to the abdominal wall with plasters in order to avoid compressing the ventral suture line.

The first dressing was opened on the third postoperative day in the absence of any bleeding or wetting. Following dressing placement, patients were discharged if they were staying nearby, and were called back for follow-up on the second day. If patients lived in rural areas and it was not possible for them to reach hospital quickly, they were hospitalized until removal of the urethral stent.

The technique we apply is quite simple. The suture that was put on the incision between the glans apex and mea provides the placement of the urethral stent in glans and the creation of two appropriate wings on both sides of glans. The depth of this incision must be so adjusted that the urethral stent can be easily inserted and so that it forms sufficient glandular wings for easy closure of the glans. Even if the cosmetic appearance of the glans appears compromised following this incision, a very acceptable esthetic appearance is restored after circumcision and flap reversal. The glans is closed in two layers in our technique. This prevents both opening of the glans and also fistula formation. Moreover, the desired cosmetic appearance of the glans can thus be achieved. The dressings were not opened except in case of bleeding on the third day postoperatively, and care was taken to keep them immobile. Rifamycin was used in the dressing.

In conclusion, the technique used in our clinic can easily be applied in the treatment of all forms of distal hypospadias. We think that it represents a significant therapeutic option in distal hypospadias surgery since, in addition to being easy to perform; it also has low complication rates and provides satisfactory cosmetic and functional outcomes.

REFERENCES

Bouty, A., Ayers, K.L., Pask, A., Heloury, Y., Sinclair, A.H., 2015. The genetic and environmental factors underlying hypospadias. Sex. Dev. 9, 239-259.

Bush, N.C., Holzer, M., Zhang, S., Snodgrass, W., 2013. Age does not impact risk for urethroplasty complications after tubularized incised plate repair of hypospadias in prepubertal boys. J. Pediatr. Urol. 9, 252-256.

Bush, N.C., Villanueva, C., Snodgrass, W., 2015. Glans size is an independent risk factor for urethroplasty complications after hypospadias repair. J. Pediatr. Urol. 11, 351-355.

da Silva, E.A., Lobountchenko, T., Marun, M.N., Rondon, A., Damiao, R., 2014. Role of penile biometric characteristics on surgical outcome of hypospadias repair. Pediatr. Surg. Int. 30, 339-344.

Duckett, J.W., 1989. Hypospadias. Pediatr. Rev. 11, 37-42.

Elganainy, E.O., Abdelsalam, Y.M., Gadelmoula, M.M., Shalaby, M.M., 2010. Combined Mathieu and Snodgrassure throplasty for hypospadias repair: A prospective randomized study. Int. J. Urol. 17, 661-665.

Hueber, P.A., Antczak, C., Abdo, A., Franc-Guimond, J., Barrieras, D., Houle, A.M., 2015. Long-term functional outcomes of distal hypospadias repair: a single center retrospective comparative study of TIPs, Mathieu and MAGPI. J. Pediatr. Urol. 11, 68.

Keays, M.A., Dave, S., 2017. Current hypospadias management: Diagnosis, surgical management, and long-term patient-centred outcomes. Can. Urol. Assoc. J. 11, 48-53.

Park, J.M., Faerber, G.J., Bloom, D.A., 1994. Long-term outcome evaluation of patients outgoing the MAGPI procedure. J. Urol. 152, 1229-1231.

Pfistermuller, K.L., McArdle, A.J., Cuckow, P.M., 2015. Meta-analysis of complication rates of the tubularized incised plate (TIP) repair. J. Pediatr. Urol. 11, 54-59.

Riedmiller, H., Androulakakis, P., Beurton, D., Kocvara, R., Gerharz, E., 2001. European Association of EAU guidelines on paediatric urology. Eur. Urol. 40, 589-599.

Snodgrass, W., 1994. Tubularized, incised plate urethroplasty for distal hypospadias. J. Urol. 151, 464-465.

Snodgrass, W.T., Bush, N., Cost, N., 2010. Tubularized incised plate hypospadias repair for distal hypospadias. J. Pediatr. Urol. 6, 408-413.

Van der Horst, H.J., de Wall, L.L., 2017. Hypospadias, all there is to know. Eur. J. Pediatr. 176, 435-441.

Warren, S., Nicol, B., 2016. Primary hypospadias repair techniques: A review of the evidence. Urol. Ann. 8, 403-408.

Weber, D.M., Schonbucher, V.B., Gobet, R., Gerber, A., Landolt, M.A., 2009. Is there an ideal age for hypospadias repair? A pilot study. J. Pediatr. Urol. 5, 345-350.

Wilkinson, D.J., Farrelly, P., Kenny, S.E., 2012. Outcomes in distal hypospadias: A systematic review of the Mathieu and tubularized incised plate repairs. J. Pediatr. Urol. 8, 307-312.

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Original Article

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Clinical impact of lung age on postoperative complications and prognosis in patients aged > 60 years with non-small cell lung cancer and no comorbidities treated by anatomical resection

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ABSTRACT

Lung age formula proposed by Morris and Temple aimed to contribute toward smoking cessation programme and it was developed by Japanese Respiratory Society. It is considered as an important useful factor for predicting postoperative respiratory complications and survival in surgically treated patients with non small cell lung cancer. As the first for Turkish society, we aimed to evaluate clinical impact of lung age on postoperative complications in patients with NSCLC aged > 60 y. Survey included anatomically resected 80 NSCLC patients aged > 60 y in OMU Thoracic Surgery Clinic between years 2005 - 2015. Three groups were created using age groups <0, 0-10, >10, calculated as the difference between lung age and true age. Lung age was calculated according to Japanese Respiratory Society formula. Preoperative, intraoperative and postoperative prognostic factors were compared between three groups. Patient numbers in three groups were 18, 17 and 45. In preoperative factors gender, smoking, FEV1, FVC, SCC was related to lung age; postoperative respiratory complications and postoperative readmission related to respiratory complications were seen to have significant association with lung age. Lung age can be used as a clinical parameter to predict postoperative complication risk for NSCLC.

1. Introduction

Lung cancer (LC) is the most common cause of death from cancer worldwide (Morris and Temple, 1985). The number of patients with LC is relatively high due to long-term smoking, aging of the population, and various environmental factors. Smoking increases the descent velocity of forced expiratory volume in 1 second (FEV1).

Morris and Temple proposed a lung age formula to motivate smoking cessation, where smoking cessation has an important beneficial effect on pulmonary function (Morris and Temple, 1985). A lung age calculation was discussed at a meeting of Japanese Respiratory Society

(JRS) members in 2001, and lung age was calculated using a reverse equation created to imagine the reference value of forced expiratory volume in one second (Weinberger, 1992; Aizawa et al., 2007).

Yamaguchi et al. proposed alternative equations for calculating lung age based on a wider range of pulmonary function test values, to reduce error in lung age calculations (Yamaguchi et al., 2011).

Lung age can be easily understood by both clinicians and patients, and allows the difference between lung age and real age to be used for predicting pulmonary complications. However, there have been few reports regarding the usefulness of lung age in LC surgery.

2. Materials and methods

Ethical approval for this study was obtained from Ondokuz Mayis University (OMU) Medical Research Ethical Committee (Approval No. OMU KAEK 2015/475, issued December 24, 2015). The study population consisted of 80 patients aged > 60 years with stage 3a or lower non-small cell lung cancer (NSCLC), treated by anatomical resection at Ondokuz Mayis University Thoracic Surgery Service. The patients were divided into three groups according to the difference between lung age and chronological age: Group 1, age gap < 0 (n = 18); Group 2, age gap 0–10 years, n = 17; and Group 3, age gap > 10 years (n = 45). To evaluate the prognostic importance of lung age, patients with diabetes mellitus, chronic liver disease, renal insufficiency, serious arrhythmias, ischemic heart disease, collagen tissue disease, or non-pulmonary malignancies were excluded from the study.

The JRS formula, which has been widely adopted in clinical investigations, was applied to our population:

Males: lung age = 0.036 × height (cm) – 1.178 – FEV1 (L)/0.028

Females: lung age = 0.022 × height (cm) – 0.005 – FEV1 (L)/0.022

The prognostic value of lung age was compared among the three groups. The requirement for informed consent was waived due to the retrospective design of the study.

Statistical analyses were performed using SPSS for Windows software (Version 20.0; SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to evaluate the normality of the data distribution. Continuous and categorical variables were analyzed using Student's t test for comparison of two groups. Comparisons of more than two groups on categorical variables were performed using analysis of variance (ANOVA) and the Kruskal–Wallis H test. Associations between categorical variables were investigated with the Chi-square, N-Par, or Fisher's exact test. The survival data of the three groups were analyzed using the log-rank, Breslow, and Kaplan–Meier tests. In all analyses, $p < 0.05$ was taken to indicate statistical significance.

3. Results

The overall cohort comprised 6 (7.6%) females and 73 (92.4%) males. Group 1 was composed of 5 (29.4%) females and 12 (70.6%) males. Group 2 was composed of 1 female (70.6%) and 16 (94.1%) males. All 45 (100%) of the patients in Group 3 were male. Larger age gaps were associated with a significant decrease in the proportion of females and a significant increase in the proportion of males ($p = 0.000$).

The average chronological age was 67.1 years in Group 1, 66.4 years in Group 2, and 66.7 years in Group 3. There was no significant association between lung age and chronological age ($p = 0.934$). The average lung age was 62.1 years in Group 1, 71.7 years in Group 2, and 86.9 years in Group 3. Lung age increased significantly with increasing age gap ($p = 0.000$), while no significant association was observed with chronological age or age gap.

Number of smokers, FEV1, and percentage forced vital capacity (%FVC) were compared among the age gap groups. The average FEV1 was 54.42% in Group 1, 56.35% in Group 2, and 28.94% in Group 3. The average %FVC was 38.89% in Group 1, 40.41% in Group 2, and 41.18% in Group 3. The average of FVC was 49.94 in Group 1, 49.24 in Group 2, and 33.42 in Group 3. The

Table 1. Distribution of histologic subtypes among groups.

			Groups			Total
			x<=0	0<x<=10	x>10	x<=0
Histology	Adenocancer	Number	10	4	15	29
		% in Group	55.6%	23.5%	33.3%	36.3%
	Squamous cell cancer		6	9	25	40
		% in Group	33.3%	52.9%	55.6%	50.0%
	Large cell NE tumor		0	0	2	2
		% in Group	0%	0%	4.4%	2.5%
	Adenosquamous cell cancer		0	1	3	4
		% in Group	0%	5.9%	6.7%	5.0%
	Bronchoalveoler cancer		0	2	0	2
		% in Group	0%	11.8%	0%	2.5%
	Less differentiated cancer		1	0	0	1
		% in Group	5.6%	0%	0%	1.3%
	Sarcomatoid cancer		1	0	0	1
		% in Group	5.6%	0%	0%	1.3%
	Inflammatory pseudotumor		0	1	0	1
		% in Group	0%	5.9%	0%	1.3%
Total			18	17	45	80
		% Group	100%	100.0%	100.0%	100.0%

average of number of smokers was 24.92 in Group 1, 41.44 in Group 2, and 45.52 in Group 3. Smoking was significantly associated with lung age (p = 0.005). FEV1 and FVC decreased significantly with increasing average lung age (p = 0.000 and p = 0.008, respectively). There was no significant association between lung age and %FVC (p = 0.939).

The distribution of histopathological subtypes among the groups is illustrated in Table 1.

As the age gap increased, the rate of squamous cell cancer (SCC) diagnosis increased significantly, while that of adenocarcinoma diagnosis decreased significantly (p = 0.037). Large cell neuroendocrine (NE) tumor diagnosis was not associated with age gap.

The association of age gap with disease stage was also investigated. Stage 1a was seen in 11.1% (n = 2) of Group 1 patients, 23.5% (n = 4) of Group 2 patients, and 17.8% (n = 8) of Group 3 patients. Stage 1b was seen in 44.4% (n = 8) of Group 1 patients, 35.3% (n = 6) of Group 2 patients, and 26.7% (n = 12) of Group 3 patients. Stage 2a was seen in 16.7% (n = 3) of Group 1 patients, 5.9% (n = 1) of Group 2 patients, and 11.1% (n = 5) of Group 3 patients. Stage 2b was seen in 11.1% (n = 2) of Group 1 patients, 23.5% (n = 4) of Group 2 patients, and 26.7% (n = 12) of Group 3 patients. Stage 3a was in 16.7% (n = 3) of Group 1 patients, 11.8% (n = 2) of Group 2 patients, and 17.8% (n = 8) of Group 3 patients. Disease stage was not significantly related to age gap in the present study (p = 0.794).

In our analyses, although the increases in lung age and resection volume were directly proportional, the association was not statistically significant (p = 0.336) (Table 2).

Table 2. Distribution of resection volume among groups.

		Groups			Total
		x<=0	0<x<=10	x>10	x<=0
Lobectomy	Number	11	13	25	49
	% in Group	64.7%	76.5%	55.6%	62.0%
Bilobectomy	Number	2	1	8	11
	% in Group	11.8%	5.9%	17.8%	13.9%
Pneumonectomy	Number	3	3	10	16
	% in Group	17.6%	17.6%	22.2%	20.3%
Segmentectomy	Number	1	0	2	3
	% in Group	5.9%	0%	4.4%	3.8%
Total	Number	18	17	45	80
	% in Group	100.0%	100.0%	100.0%	100.0%

The associations of duration of operation, duration of drain withdrawal, and duration of hospitalization with lung age were investigated. Neither duration of operation nor duration of drain withdrawal showed a significant association with lung age (p = 0.608 and p = 0.708, respectively). The duration of hospitalization increased with increasing lung age, but the association was not statistically significant (p = 0.522).

The rate of postoperative intensive care unit (ICU) hospitalization for 1 day was 100% (n = 9) in Group 1, 100% (n = 9) in Group 2, and 84.2% (n = 16) in Group 3. The rate of postoperative ICU hospitalization for 2 days was 0% in Groups 1 and 2 and 10.5% (n = 2) in Group 3. No patients in Group 1 or 2 were hospitalized in the ICU within 3 days postoperatively, while the rate in Group 3 was 5.3% (n = 1). As age gap increased, the rate of postoperative ICU hospitalization also increased, but not statistically significantly (p = 0.129).

Postoperative intubation was performed in 46.2% (n = 6) of patients in Group 1, 0% (n = 0) in Group 2, and 53.8% (n = 7) in Group 3. Postoperative extubation was performed in 18% (n = 11) of patients in Group 1, 26.2% (n = 16) in Group 2, and 55.7% (n = 34) in Group 3. The association between age gap and postoperative intubation status was significant (p = 0.029).

There was a significant association between the rate of postoperative respiratory complications and age gap (p = 0.013) (Table 3).

Table 3. Distribution of histologic subtypes among groups.

			Groups			Total
			x<=0	0<x<=10	x>10	x<=0
Respiratory Complications	Expansion defect	Number	0	1	6	7
		% in Total	0%	14.3%	85.7%	100.0%
	Prolonged air leak	Number	4	2	6	12
		% in Total	33.3%	16.7%	50.0%	100.0%
	Dyspnea	Number	0	1	0	1
		% in Total	0%	100.0%	0%	100.0%
	Bronchopleural fistula	Number	0	1	0	1
		% in Total	0%	100.0%	0%	100.0%
	Recycling in sputum	Number	0	0	2	2
		% in Total	0%	0%	100.0%	100.0%
	Subcutaneous empysema	Number	0	0	1	1
		% in Total	0%	0%	100.0%	100.0%
	Respiratory arrest	Number	0	0	1	1
		% in Total	0%	0%	100.0%	100.0%
	Empyema	Number	0	1	0	1
		% in Total	0%	100.0%	0%	100.0%
	Haemorragic drainage	Number	0	1	0	1
		% in Total	0%	100.0%	0%	100.0%
Total		% in Total	14.8%	25.9%	59.3%	100.0%

Postoperative pleurodesis was performed in 7.7% (n = 1) of patients in Group 1, 0% (n = 0) in Group 2, and 23.1% (n = 3) in Group 3. Pleural aspiration was applied in 7.7% (n = 1) patients in Group 1, 15.4% (n = 15.4) in Group 2, and 30.8% (n = 4) in Group 3. The Heimlich valve was used in 7.7% (n = 1) of patients in Group 1, 0% (n = 0) in Group 2, and 7.7% (n = 19) in Group 3. As the age gap increased, so too did the rates of postoperative pleurodesis, pleural aspiration and Heimlich valve use (p = 0.092).

Postoperative nonpulmonary complications (cardiac arrhythmia, hypertension, ischemic heart disease), infection (wound infection), neurological sequelae (delirium), and urological symptoms (hematuria) were observed in 22.2% (n = 6) of patients in Group 1, 25.9% (n = 7) in Group 2, and 51.9% (n = 14) in Group 3. The rates of postoperative nonpulmonary complications increased with increasing age gap although the association was not statistically significant (p = 0.649). Readmission to hospital with pulmonary pathology was significantly associated with age gap (p = 0.022) (Table 4).

Table 4. Distribution of readmission to hospital with respiratory complications.

		Groups			Total
		x<=0	0<x<=10	x>10	x<=0
Readmission to hospital with respiratory complications					
Pneumonia	Number	1	1	2	4
	% in Groups	5.9%	5.9%	4.5%	5.1%
Dyspnea	Number	1	0	2	3
	% in Groups	5.9%	0%	4.5%	3.8%
Pleural effusion	Number	0	1	0	1
	% in Groups	0%	5.9%	0%	1.3%
Bronchopleural fistula	Number	0	0	3	3
	% in Groups	0%	0%	6.8%	3.8%
Empyema	Number	0	0	2	2
	% in Groups	0%	0%	4.5%	2.6%
Lung abscess	Number	0	0	1	1
	% in Groups	0%	0%	2.3%	1.3%
Pulmonary th-romboembolism	Number	1	0	0	1
	% in Groups	5.9%	0%	0%	1.3%
Total	Number	18	17	45	80
	% in Groups	100.0%	100.0%	100.0%	100.0%

The rates of readmission to hospital with nonpulmonary pathology (cardiac arrhythmia, hypertension, ischemic heart disease), infection (wound infection), neurological sequelae (delirium), and urological symptoms (hematuria) were 41.2% (n = 7) in Group 1, 35.3% (n = 6) in Group 2, and 27.2% (n = 12) in Group 3. There was no significant association between lung age and readmission to hospital with nonpulmonary etiology (p = 0.727).

The association between postoperative survival and lung age was evaluated as shown in Figure 1. Postoperative survival decreased with increasing age gap, but the association was not statistically significant (p = 0.253).

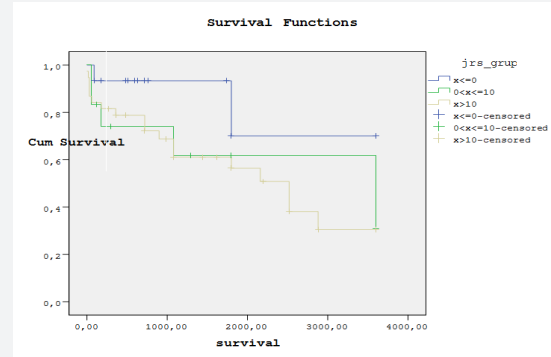

Fig. 1. Analyses of postoperative survival among groups.

4. Discussion

Surgery is the best treatment modality for early phase NSCLC, but postoperative morbidity and mortality are major problems for thoracic surgeons especially after surgical resection of NSCLC patients with chronic obstructive pulmonary disease (COPD). Evaluation of surgical prognosis requires knowledge of preoperative risk factors and postoperative morbidity and mortality rates. To evaluate lung function, the concept of lung age can be applied, where a lung age older than the chronological age indicates weak lung function.

In our study, we grouped the patients according to lung age and age gap (between lung and chronological age), because lung age can increase with the decreases in FEV1 seen with increasing chronological age. The age gap can also be applied as a standardized measurement to any age group, as demonstrated in the literature (Ogawa et al., 2014).

The JRS formula, which has been adopted in many clinical investigations, was used in our study. Similar to previous reports, there was a significant increase in the proportion of male patients with increasing age gap. In the present study, lung age also increased significantly with increasing age gap, similar to previous reports. However, in contrast to the literature, chronological age and age gap did not show a significant association in the present study (Ogawa et al., 2014).

As in previous studies, smoking was significantly related to age gap in the present study, with smokers showing a markedly advanced lung age compared to chronological age (Haruki et al., 2010; Ogawa et al., 2014). In our study, FEV1 and FVC decreased significantly with increasing lung age, but %FVC and lung age did not show a significant association. Ogawa et al. reported that lung age decreased as FEV1 increased, but not statistically significantly (Ogawa et al., 2014). To our knowledge,

there have been no other studies regarding the relations of lung age with FVC and %FVC.

In the present study, the rate of SCC diagnosis increased significantly, while the rate of adenocarcinoma diagnosis decreased significantly, with increasing age gap. In addition, NE tumor diagnosis was not significantly associated with age gap, as in previous reports.

Similar to previous reports, age gap and disease stage did not show a significant association in the present study; Ogawa et al. reported that increases in lung age and disease stage were directly proportional (Haruki et al., 2010; Ogawa et al., 2014). As in the present study, increased lung age and resection volume were reported previously to be associated, although the relationship was not statistically significant (Haruki et al., 2010; Ogawa et al., 2014).

There was no significant association of duration of operation with lung age, or of duration of chest tube withdrawal with lung age, in our study or in the literature (Ogawa et al., 2014). Previously, the duration of hospitalization was reported to increase with increasing lung age (Ogawa et al., 2014), while in the present study that association was not statistically significant.

In the present study, length of ICU stay also increased with increasing lung age, but this relationship was not statistically significant. Postoperative respiratory complications were significantly associated with lung age, as reported previously (Ogawa et al., 2014). The rate of pleural adhesion also increased with increasing age gap, but this relationship was not statistically significant.

Similarly, it was reported that nonrespiratory complications also increased with increasing lung age (Ogawa et al., 2014). Readmission to hospital with respiratory and nonrespiratory complications also increased with increasing age gap in the present study, similar to the report by Ogawa et al. (2014).

Preoperative pulmonary physiotherapy, preoperative bronchodilator therapy, effective bronchial lavage, smoking cessation programs, etc., can markedly reduce rates of postoperative readmission to hospital. Especially in NSCLC patients aged > 60 years (particularly those with COPD), lung age should be calculated to predict the likelihood of postoperative complications and enhance prognostic accuracy.

In the present study, patients with an age gap > 10 years showed significantly increased rates of postoperative complications and readmission to hospital; thus, special attention should be paid to such patients.

Although lung age is a simple and effective way to determine patient status, the calculation thereof is prone to error. FEV1 can decrease in nonsmoking patients with asthma, pulmonary fibrosis, obesity, or neuromuscular disease, and it is unclear how best to determine the lung age in such patients. This is because it remains unclear how to measure the effects of factors other than smoking on a smoker's lung age where, if the FEV1 cannot be evaluated accurately, estimated lung age will be prone to error.

This study had some limitations. First, it used a retrospective design, and 32.5% of the patients died due to recurrent cancer or other diseases. Thus, prospective data are needed to support our findings. Further studies aimed at predicting long-term outcomes using regression equations specific to the Turkish population are also necessary. Nevertheless, our study suggests a model for predicting postoperative complications in older patients with NSCLC.

The age gap between chronological age and lung age was significantly associated with postoperative complications in univariate analysis, and was shown to be an independent predictor of complications in multivariate analysis. Lung age should be investigated in more detail as a potential predictor of both postoperative complications and prognosis. This parameter could help both patients and clinicians to gain a better understanding of pulmonary function.

REFERENCES

Aizawa, H., Kudoh, S., 2007. Proposal for 'lung age' to explain impairment of pulmonary function. Prog. Med. 27, 2418-2423.

Haruki, T., Nakamura, H., Taniguchi, Y., Miwa, K., Adachi, Y., Fujioka, S., 2010. "Lung age" predicts post-operative complications and survival in lung cancer patients. Respirology. 15, 495-500.

Morris, J.F., Temple, W., 1985. Spirometric "lung age" estimation for motivating smoking cessation. Prev. Med. 14, 655-662.

Ogawa, F., Miyata, S., Nakashima, H., Matsui, Y., Shiomi, K., Iyoda, A., Satoh, Y., 2014. Clinical impact of lung age on postoperative complications in non small cell lung cancer patients aged > 70 y. J. Surg. Res. 188, 373-380.

Ogawa, F., Satoh, Y., Iyoda, A., Amano, H., Kumagai, Y., Majima, M., 2015. Clinical impact of lung age on postoperative readmission in non small cell lung cancer. J. Surg. Res. 193, 442-448.

Weinberger, Chronic Obstructive Pulmonary Disease, Principles of Pulmonary Medicine, 4th edition 1992.

Yamaguchi, K., Onizawa, S., Tsuji, T., Aoshiba, K., Nagai, A., 2011. How to evaluate "spirometric" lung age – what method is approvable? Respir. Physiol. Neurobiol. 178, 349–351.

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Case Report

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A case of enoxaparin-related spontaneous retroperitoneal hematoma in an elderly patient

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ABSTRACT

Enoxaparin is a low molecular weight heparin and the most commonly used antithrombotic agent worldwide. However, this is also leading to increasing incidences of complications. One of the thesecomplication is spontaneous retroperitoneal hematoma. The aim of the present study is to evaluate spontaneous retroperitoneal hematoma associated with enoxaparin use in an 86-year-old man hospitalized for seven days with a diagnosis of chronic obstructive pulmonary disease. The usage of enoxaparin with antiplatelet agents increased the risk of bleeding in an 86-year-old patient. The usage of combination of enoxaparin and antiplatelet medications should be paid more attention.

1. Introduction

Spontaneous retroperitoneal hematoma (SRPH) is a rare, but life-threatening condition. Appropriate treatment relies based on prompt and accurate diagnosis. This is quite simple using imaging techniques. However, it may not always be easy to identify the source of the hemorrhage and the pathological state responsible.

The most commonly reported etiology of SRPH involves hemorrhages of renal cell carcinomas and angiomyolipoma, which constitute 57-72% of all cases. Other vascular causes of SRPH include polyarteritis nodosa, renal artery aneurysm, and necrotizing arteritis. SRPH has been well described among patients receiving anticoagulant therapy, and has been linked to warfarin, low molecular weight heparin (enoxaparin) and ticlopidine (Daliakopoulos, 2011).

We report a case of SRPH in an elderly patient with chronic obstructive pulmonary disease (COPD) and impaired kidney function receiving anticoagulant therapy.

2. Case report

An 86-year-old man presented to the chest diseases clinic with respiratory difficulty, cough, and generally impaired condition. In addition to COPD treatment, the patient was also receiving heart failure treatment and

antiaggregant therapy. He was admitted to the clinic. The patient was receiving digoxin 0.25 mg, enoxaparin 6000 IU, methylprednisolone 40 mg, acetylcysteine 300 mg, and acetyl silicic acid 100 mg, and was began ceftriaxone 1 g for infection treatment. On the seventh day of treatment, the patient described abdominal and left flank pain, and hypotension (80/50 mmHg) and tachycardia (135/min) developed. Control blood count decreased to 6.8 g/dl. The patient was given enoxaparin and acetyl silicic acid. His platelet count was 285.000/mm^3, INR 0.94, Prothrombin time (PT) 10.2 s, activated partial prothrombin time (APTT) 20.9 s, urea 173 mg/dl, creatinine 3.2 mg/dl and potassium 6.6 mEq/L. Emergency abdominal tomography revealed a retroperitoneal solid mass area, 110 x 70 mm in size, potentially compatible with hematoma contiguous and anterior to the left iliopsoas muscle, at the left infrarenal level (Fig. 1).

Antifactor Xa was one of the most important indicators to monitor the effect of low-molecular anticoagulants but could not be measured due to lack of equipment in the hospital. Emergency consultation was performed with the urology department on suspicion of retroperitoneal hematoma. When first consultation of urology department, his general condition was poor, and hypotension and urine retention were present. The patient was urgently transferred to the medical intensive care unit. Enoxaparin was discontinued, and the patient was given four units of erythrocyte suspension and three units of plasma. Since no more than 12 hours after the last dose of enoxaparin, the patient was administered 50 mg protamine sulfate. Respiration stopped, and he was intubated. Despite blood product transfusion and supportive treatment, death occurred 48 hours later.

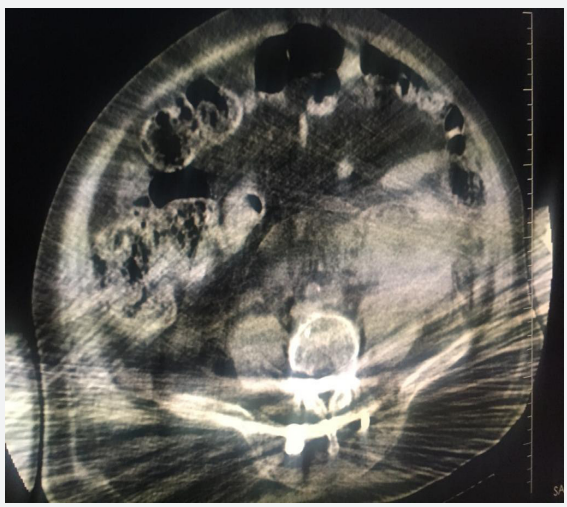

Fig. 1. Abdominal tomography revealed a retroperitoneal solid mass area, 110 x 70 mm in size, potentially compatible with hematoma contiguous and anterior to the left iliopsoas muscle, at the left infrarenal level.

3. Discussion

Tumors are the most common cause of SRPH. Enoxaparin-related SRPH is a rare entity (Vaya et al., 2003). Enoxaparin has been shown to as safe and effective as unfractionated heparin in the treatment of venous thrombosis. However, various significant complications such as acute pulmonary embolism, abdominal wall hematoma, psoas hematoma, femoral hematoma, and retroperitoneal hematoma have been reported in patients treated with enoxaparin for acute venous thromboembolism. The common feature in these cases is advanced age (Vaya et al., 2003). Enoxaparin therapy has been shown to be a risk factor for hematoma over the age of 70. An age-related decrease in glomerular filtration rates in elderly patients has been reported to result in a decrease in medication sensitivity through decreased drug clearance and a decrease in drug levels (Ernits et al., 2005).

Symptoms and findings of SRPH depend on the etiology. Immediate hypovolemic shock occurs in severe hematomas, and Grey Turner's sign may develop. The optimal method in the diagnosis of SRPH is abdominal pelvic tomography (Lissoway and Booth, 2010). Acute abdominal pain and a sudden fall in hemoglobin should suggest the possibility of SRPH. In terms of treatment, anticoagulant therapy must be stopped. Blood transfusion may be required, depending on hematocrit values. If the hemorrhage cannot be stabilized with support treatment and all interventions are unsuccessful, surgery may be required. SRPH may sometimes give rise to abdominal compartment syndrome by compressing surrounding tissues and organs, and this can only be corrected surgically (Haq et al., 2010; Daliakopoulos, 2011). In our case, anticoagulant therapy was immediately discontinued, but the patient's condition worsened rapidly, there was not enough time for surgical intervention. Abdominal compartment syndrome is not an unexpected finding due to the patient's advanced age, uremic status and development of COPD.

In addition, the use of enoxaparin together with antiplatelet agents increases the risk of bleeding. Intraocular and intracranial bleeding, and retroperitoneal bleeding-related mortality in one patient, has been reported in cases in which enoxaparin and acetyl silicic acid was used in combination (Haq et al., 2010). Our patient received both enoxaparin and acetyl silicic acid for seven days during hospitalization. These drugs may be one cause of the bleeding.

We report a case of retroperitoneal hematoma with no change in coagulation parameters in a patient receiving enoxaparin and acetyl silicic acid for the treatment of venous thrombosis. However, we think that the patient's advanced age, impaired kidney functions and development of COPD led to the development of retroperitoneal hematoma and subsequent rapid progression.

In conclusion, anticoagulant therapy with enoxaparin can lead to severe hematoma. It should therefore be remembered that when enoxaparin is used together with antiplatelet medications such as acetyl silicic acid, particularly in the elderly and in patients with impaired kidney functions, this increases the risk of hemorrhage. Greater care must be taken over the use of these drugs, particularly in the advanced age group. Further studies are therefore needed in order to determine the appropriate dose range in elderly subjects without compromising therapeutic effectiveness in acute thromboembolic patients.

REFERENCES

Daliakopoulos, S.I., 2011. Spontaneous retroperitoneal hematoma: A rare devastating clinical entity of a pleiada of less common origins. Surgery Tech. Case Rep. 3, 8-9.

Ernits, M., Mohan, P.S., Fares, L.G., Hardy, H., 2005. A retroperitoneal bleed induced by enoxaparin therapy. Am. Surg. 71, 430-433.

Haq, M., Taimur, S., Khan, S., Rahman, M., 2010. Retroperitoneal hematoma following enoxaparin treatment in an elderly woman- A case report. J. Cardiol. 3, 94-97.

Lissoway, J., Booth, A., 2010. Fatal retroperitoneal hematoma after enoxaparin administration in a patient with paroxysmal atrial flutter. Am. J. Health Syst. Pharm. 67, 806-809.

Vaya, A., Mira, Y., Aznar, J., 2003. Enoxaparin-related fatal spontaneous retroperitoneal hematoma in the elderly. Thromb. Res. 110, 69-70.

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Case Report

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An unusual case of asymptomatic diffuse alveolar hemorrhage related to amiodarone induced INR elevation

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ABSTRACT

Pulmonary adverse effects of amiodarone are among the important causesof morbidity. Such effects may rarely manifest as diffuse alveolar hemorrhage. Another important amiodarone-induced adverse effect is hepatotoxicity. Hepatotoxicity mostly presents as asymptomatic elevation of the liver enzymes. To the best of our knowledge, in amiodarone-induced hepatotoxicity, AST and ALT elevations are well known; however, there are no clear data regarding the high International Normalized Ratio (INR) levels in such a condition. In the present report, we describe the case of a patient under management with chronic low-dose amiodarone, who was admitted to the emergency department for lingual hematoma. During the assessment for bleeding diathesis, the INR was found to be 8.59. After excluding all other possible causes for the high INR level, amiodarone was suggested to be the cause. Since there were diffuse infiltrations on chest x-ray, the patient underwent thorax tomography. Asymptomatic diffuse alveolar hemorrhage secondary to INR elevation was considered. This patient is the first case who had amiodarone-induced INR elevation, and as a consequence, developed asymptomatic diffuse alveolar hemorrhage.

1. Introduction

Amiodarone is one of the anti-arrhythmic medications frequently used in the treatment of ventricular and supraventricular tachycardia. It has a long half-life and accumulates in adipose tissue especially during chronic use (Goldschlager et al., 2007). As with other anti-arrhythmic medications, it has important adverse effects limiting its use and causing increase in morbidity and mortality (Qin et al., 2015). Among these, the commonly known adverse effects are thyroid dysfunction, corneal micro deposits in eyes, blue-looking skin, and toxicity to brain, liver, and lungs (Podrid, 1995). Patients using amiodarone should be monitored regularly for adverse effects (Haverkamp et al., 2017). Here, we report a case of amiodarone toxicity in a 76-year-old male patient presenting with diffuse alveolar hemorrhage and lingual hematoma.

2. Case report

A 76-year-old male patient was admitted to the emergency department with lingual hematoma. He was conscious, cooperative, and his vital signs were stable. On physical examination, he had blue-gray skin discoloration, lingual hematoma (Fig. 1A), corneal micro deposits (Fig. 1B), bilaterally rough inspiratory crackles at the base of the lungs and mild systolic murmur over the left lower sternal border. His medical history involved type 2 diabetes, coronary stent, ICD implantation, and frequent

hospitalization for heart failure. He was taking 60 mg/day gliclazide, 100 mg/day acetylsalicylic acid, 5 mg/day Ramipril, 25 mg/day spironolactone, 0.25 mg/day digoxin and 200 mg/day amiodarone. ECG showed sinus rhythm with left bundle branch block. Transthoracic echocardiography revealed left ventricle systolic dysfunction with an ejection fraction of 25%, moderate biventricular and biatrial dilatation, and mild mitral and moderate tricuspid valve insufficiency. Blood tests on admission showed the following results; Hg, 11.5gr/dL; WBC count, 8.39/mm3; platelet count, 136.000/mm3; glucose, 404 mg/dL; urea, 39.4mg/dL; creatinine, 0.92mg/dL; CRP, 18.89 mg/L; and serum digoxin, 0.9 ng/ml. He was not on any anticoagulant agent and his INR level was 8.59. Bilateral diffuse alveolar density accompanied by diffuse opacities were noted on chest x-ray examination (Fig. 2A). After initial evaluation, he was hospitalized with the suspicion of amiodarone-induced diffuse alveolar hemorrhage. Thoracic computerized tomography (CT) confirmed bilateral diffuse alveolar densities, consistent with alveolar hemorrhage (Fig. 2C). His TSH, T4, and T3 levels were 0.06 IU/mL, 2.10 ng/ dL, and 1.89 pg/mL respectively, suggesting amiodarone-induced thyrotoxicosis. Amiodarone treatment was discontinued, and fresh frozen plasma was administered for high INR levels. Vitamin K administration was found to be ineffective for this purpose. Despite an initial decrease in INR levels after each administration of fresh frozen plasma, his INR levels returned to the baseline levels and remained high during the first ten days. Abdominal ultrasonography revealed no gross abnormality of liver or spleen. All serological and immunological tests, and tests for tumor markers were negative. After discontinuation of the amiodarone treatment, the blue-gray discoloration regressed over days (Fig. 1C). The regression in pulmonary alveolar hemorrhage was demonstrated via chest x-ray (Fig. 2B) and thoracic CT (Fig. 2D). On the 10th day of hospitalization, when INR level was 1.6, the patient was discharged from the hospital. His INR level was within the normal limit one week after discharge.

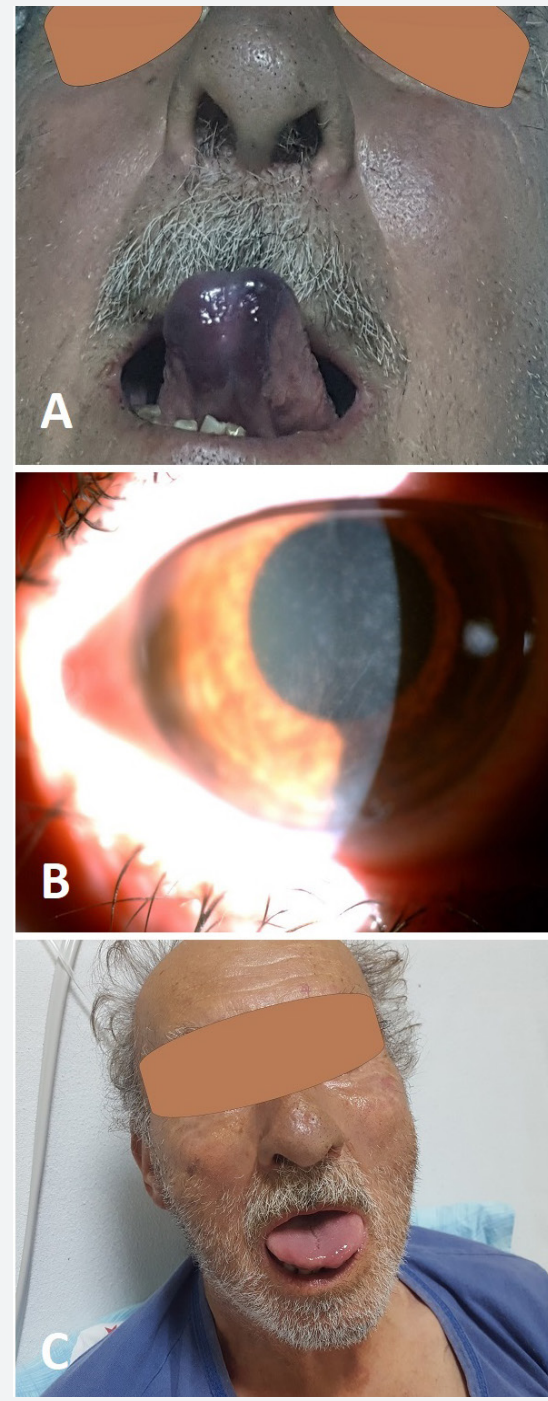

Fig. 1. A. Bluish discoloration, particularly around the mouth and the nose. B. Blue discoloration regressed. C. Corneal micro deposits.

3. Discussion

Patients using amiodarone should be assessed carefully in terms of adverse effects. Hepatotoxicity is a commonly observed adverse effect in patients using amiodarone. It manifests as the elevation of liver enzymes such as AST and ALT. In our case, amiodarone-induced hepatotoxicity manifested as INR elevation without AST or ALT elevation. For hepatotoxicity assessment in patients using amiodarone, it might be useful to check INR levels, in addition to AST and ALT levels.

Due to the lipophilic structure of amiodarone, it has a long half-life varying among patients (35–110 days) (Goldschlager et al., 2007). Therefore, the effects of amiodarone treatment may persist even after discontinuation of the treatment. In the present case, INR elevation persisted for more than 10 days despite multiple fresh frozen plasma administrations. Amiodarone-induced hepatotoxicity was probably the primary reason responsible for the INR elevation in our patient. In addition, INR elevation accompanied by other signs of amiodarone toxicity including those on skin, eyes, thyroid, brain, and lungs were other findings indicating amiodarone-induced INR elevation.

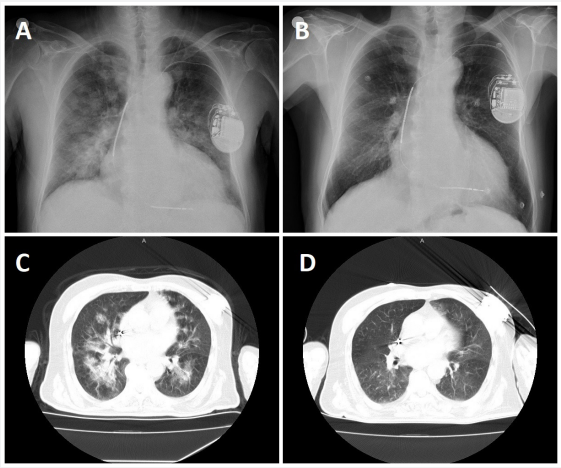

Fig. 2. A. Diffuse alveolar density with diffuse opacities on chest X-ray. B. The regression of pulmonary hemorrhage on chest X-ray. C. Diffuse alveolar density on bilateral lungs on thoracic computed tomography. D. The regression of pulmonary hemorrhage on thoracic computed tomography.

Anticoagulant and anti-platelet medications are frequently used along with amiodarone. In patients taking warfarin, amiodarone-induced INR elevation has been reported in several studies (Lu et al., 2008; Holm et al., 2017). However, in the present case, the patient was not taking warfarin and developed serious INR elevation while using amiodarone. We did not find any other reason for INR elevation. Thus, INR elevation secondary to amiodarone-induced hepatotoxicity was our primary diagnosis. In support of the present case, Sahutoğlu et al. reviewed thyrotoxicosis development and its treatment in a heart-transplant patient using amiodarone. The INR level of the patient, who was using amiodarone, was 32.8 (Sahutoglu et al., 2013). Similarly, in the present case, left ventricle functions were decreased, and the patient developed amiodarone-induced thyrotoxicosis. Decreased left ventricular functions and development of thyrotoxicosis might have been predisposing factors for amiodarone-induced INR elevation in the present case. The patient also used anti-platelet medication (100 mg acetylsalicylic acid). Acetylsalicylic acid use along with elevation of INR levels might have been related to the tongue hematoma and diffuse alveolar hemorrhage, with the effects mediated via increased bleeding risk.

Amiodarone toxicity may be associated with high INR levels and may cause life-threatening bleeding complications like diffuse alveolar hemorrhage. This should always be borne in mind in cases of patients using amiodarone, and INR levels should also be monitored in this context.

REFERENCES

Goldschlager, N., Epstein, A. E., Naccarelli, G. V., Olshansky, B., Singh, B., Collard, H. R., 2007. Electrophysiology. A practical guide for clinicians who treat patients with amiodarone. Heart. Rhythm. 4, 1250-1259.

Haverkamp, W., Israel, C., Parwani, A., 2017. Clinical aspects of treatment with amiodarone. Herzschrittmacherther Elektrophysiol. 28, 307-316. Holm, J., Lindh, J. D., Andersson, M. L., Mannheimer, B., 2017. The effect of amiodarone on warfarin anticoagulation: A register-based nationwide cohort study involving the Swedish population. J. Thromb. Haemost. 15, 446-453.

Lu, Y., Won, K. A., Nelson, B. J., Qi, D., Rausch, D. J., Asinger, R. W., 2008. Characteristics of the amiodarone-warfarin interaction during long-term follow-up. Am. J. Health Syst. Pharm. 65, 947-952.

Podrid, P. J., 1995. Amiodarone: Reevaluation of an old drug. Ann. Intern. Med. 122, 689-700.

Qin, D., Leef, G., Alam, M. B., Rattan, R., Munir, M. B., Patel, D., Saba, S., 2015. Mortality risk of long-term amiodarone therapy for atrial fibrillation patients without structural heart disease. Cardiol. J. 22, 622-629.

Şahutoğlu, C., Pestilci, Z., Kocabaş, S., Zekiye, F.A., Hepkarşı, A., Engin, Ç., 2013. Anaesthetic management in a heart transplantation patient with amiodarone associated thyrotoxicosis. GKD. Anest. Yoğ. Bak. Dern. Derg. 19, 206-210.

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Bilateral testicular metastasis of prostate adenocarcinoma: A case report

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ABSTRACT

Prostate cancer is one of the most common solid organ tumors to metastasize testis. However testicular metastases, especially bilateral testicular metastases, are rarely seen cases. We present this rare case report about a 68-year-old patient with prostate cancer presented with complaints of swelling in the testis. Physical examination and radiological imaging revealed testicular metastasis of prostate cancer. As a result we believe that if patient presents with active complaints or a mass in the testicle, we should evaluate further with scrotal ultrasonography at the time of diagnosis and follow-up. Following those, testicular biopsy or orchiectomy should be performed if seen necessary.

1. Introduction

Prostate cancer is one of the most common solid organ malignancies in male population and often metastasizes to iliac lymph nodes, bone, lungs, rarely to testes and other genitourinary system (Patel et al., 1989; Dutt et al., 2000). Among the primary foci of testicular metastases; lung, prostate, melanoma and gastrointestinal system tumors are the most common ones. In the course of prostate cancer, there has been cases reported as unilateral testicular metastases which are relatively uncommon; bilateral metastases have also been reported but more rarely. Metastatic testicular tumors need to be differentiated from testis seminoma, because in microscopical examination they retain testicular parenchyma in the intratubular, intertubular and nodular pattern. Histopathological or radiological methods are used in the differentiation of primary and metastatic testicular tumors.

2. Case report

A 68-year-old male patient who had no previously known diseases, presented our clinic with hematuria for about 2 months. In the digital rectal examination, a grade 1 nodular lesion was detected in the prostate. In laboratory findings, prostate-specific antigen (PSA) value was determined as > 100 ng/ml.. The patient

underwent prostate needle biopsy with transrectal ultrasonography. Histopathological findings are reported as prostate adenocarcinoma with Gleason score 9 (4 + 5).

The patient's abdominal computed tomography (CT) revealed a large number of lymph nodes thought to be metastatic, with a central cystic (necrotic) appearance, observed in the paraaortic area at the infrarenal level and conglomerates in both main and external iliac groups. The largest one is found within the external iliac lymph nodes, with 52*30 mm diameter. Bone scintigraphy revealed no metastasis.

The patient was started on LHRH agonist + antiandrogen therapy. After the treatment, patient's PSA values decreased to 3.94 ng / ml. After receiving the maximum androgen blockade (MAB) for 2.5 years, the patient stopped coming to examinations for 1 year.

At the first admittance to clinic after 1 year period, an increase in PSA levels was observed. Widespread abdominal lymph nodes and bone metastasis in the T7 vertebrae were detected. Docetaxel chemotherapy was inititated.

After 3 cycles of docetaxel, abdominal magnetic resonance imaging (MRI) showed minimal progression and the treatment was completed with 6 cycles. After 6 cycles of treatment, due to progression detected in abdominal MRI, enzalutamide treatment was started. After 3 month of therapy, abdominal MRI was repeated which showed increased size of the lymph nodes in the abdomen, and additionally suspicious lesions were found in the right lower lobe of the lung. As a result, cabazitaxel treatment was initiated.

After 3 cycles of treatment, abdominal MRI revealed new lesion in the abdomen and pelvis in addition to previous lesions, and LUTESIUM-177 PSMA treatment was started. 3 cycles were given. After a significant progression was detected in all foci of PET, current therapy was replaced with mitoxantron chemotherapy.

While receiving mitoxantron chemotherapy, the patient admitted to our clinic with painless mass in both testes and right groin pain in October 2018. Physical examination revealed a rigid mass in the upper lobe of the left testis and hydrocele in both testes. The patient's tumor markers (α-FP, β-HCG) were within normal limits and the PSA value was 1761 ng/ml. In ultrasonography (USG), a 5x4 mm diameter lesion in the right testis and a large sized hypoechoic lesion with a lobulated contour and rough calcifications of 11x10 mm in the left testicle were found. Because the patient had history of malignancy and no significant increase in blood flow of the testis was shown, the lesions were evaluated in favor of possible metastases.

Abdominal MRI was performed on the patient. MRI findings are similar to USG, the lesions identified in both testes were contrasted and diffusion-T2 weighted images had hypointensity similar to the present prostate lesions'. Axial T2 and T1 images showed hypointense in T2, isointense in T1, and no-limiting lesions were contrasted (arrows) (Fig. 1-6).

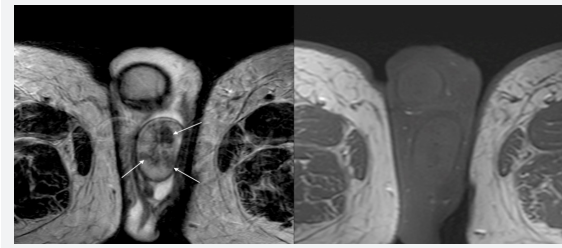

Fig. 1. Prostate cancer testis metastasis T2 T1 sequence (indicated by arrow).

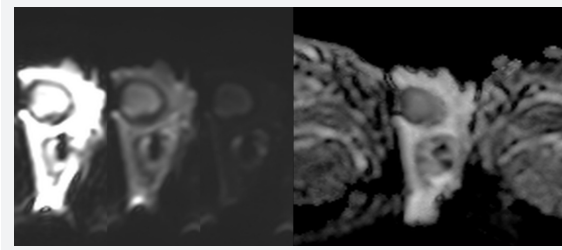

Fig. 2. Diffusion imaging of testis parenchyma.

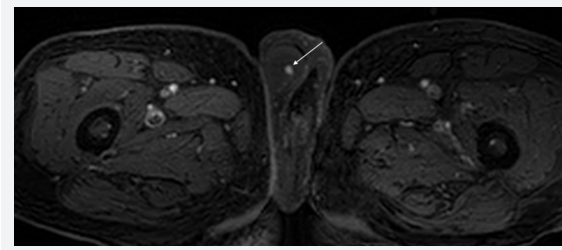

Fig. 3. Metastasis of the right testis (indicated by arrow).

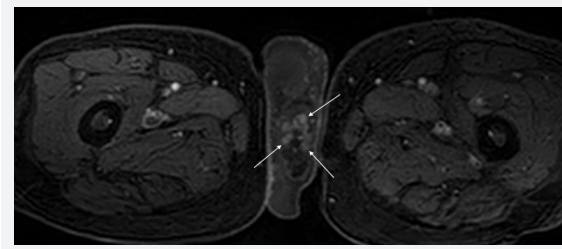

Fig. 4. Metastasis of the left testis (indicated by arrow).

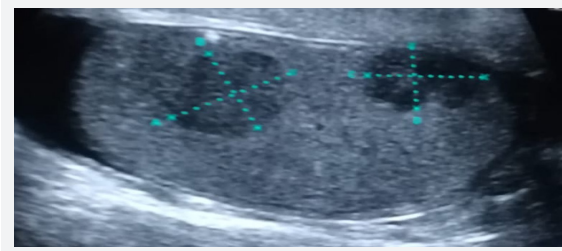

Fig. 5. USG image of left testicular lesions.

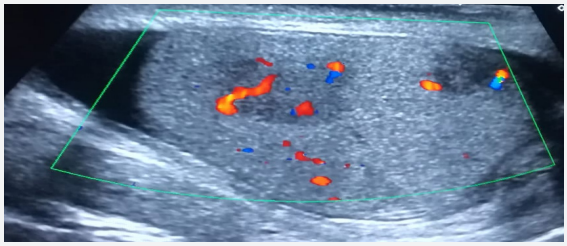

Fig. 6. Doppler USG image of the lesions in the left testis.

The lesions in the testis were concluded to be viewed as metastasis, because the primary disease was widespreadly metastatic, and the lesions in the testis had similar MRI signal characteristics and the lesions were bilateral.

Bilateral inguinal orchiectomy was not performed because it would not cause change of the treatment protocol. The current treatment of the patient was continued without making any changes.

We believe that concerning the patients with prostate cancer, who have active complaints or unusual mass in the testicle, evaluation with scrotal ultrasonography at the time of diagnosis or follow-up may be beneficial. If further investigation investigation is needed, testicular biopsy or orchiectomy could be chosen to be performed.

3. Discussion

Although prostate cancer is a common malignancy in mele popullation and has frequent metastasis, the metastasis of the testis is uncommon because of its blood-testicular barrier. Testicular metastasis of prostate cancer is rarely seen as bilateral metastasis (Richie and Steele, 2002; Manikandan et al., 2006). Frequently testicular metastasis of prostate cancer is a diagnosis found out in autopsies, since androgen blockade was not performed as often as it used to be (Grigron et al., 1896). The most common tumors metastasizing to the testis are lung, prostate, melanoma and gastrointestinal tract tumors. A study in 2000, involving 200 cases of testicular tumors, had found only 14% of the patients had metastatic tumors. In another study, the primary focus of metastases were determined as prostate in 57.1%, seminal vesicles in 7.1%, lung in 13.6% and gastrointestinal system in 14.2% (Menon et al., 2010). A seperate study examining 4012 autopsy data, showed that within all metastatic cases only 0.1% were observed in testis. In the same study, prostate was found as the primary source in 36% of the metastases in the testes (Patel et al., 1989). The metastatic spread of prostate cancer is mainly mediated by lymphovascular route (Dutt et al., 2000). The most common metastasis target of the prostate carcinoma is regional lymph nodes and the second most common being the bones. In a study of 4012 autopsy data, only 4 of 193 prostate cancer cases were found to metastasize to the testis (Patel et al., 1989).

Although testicular metastasis of prostate cancer is an uncommon clinic, it presents offen with a relatively common complaint, a non-palpable mass in the testis (Lyngdrof and Nielsen, 1987) which is also the case in our patient.

The average life expectancy of patients with prostate cancer is approximately 6-18 months, due to poor prognosis. Usually testicular metastasis occurs during the course of pre-existing cancer. Metastasis to testes may be the first finding of an undiagnosed cancer; may also be a finding of relapse after partial remissions of prostate cancer. The reason why advanced-stage prostate cancer metastasizes to an atypical location such as testicles despite being given treatment, as in our patient who had received 2 and half years hormonal therapy which was followed by 1 year of uncooperation to therapy, could be explained by the probability of the presence of resistant tumor cells which rather metastasize to atypical locations. It should be kept in mind that bone metastasis and peripheral organ metastasis as well as testicular metastasis may be rare in patients diagnosed as advanced-stage prostate cancer at the time of diagnosis.

REFERENCES

Dutt, N., Bates, A.W., Baithun, S.I., 2000. Secondary neoplasms of the male genital tract with different patterns of involvement in adults and children. Histopathology. 37, 323-331.

Grigron, D.J., Shum, D.T., Hayman, W.P., 1986. Metastatic cancer of testis. Can. J. Surg. 29, 359-361.

Korkes, F., Gasperini, R., Korkes, K.L., Silva Neto, D.C., Castro, M.G., 2009. Testicular metastases: A poor prognostic factor in patients with advanced prostate cancer. World. J. Urol. 27, 113-115.

Lyngdrof, P., Nielsen, K., 1987. Prostatic cancer with metastasis to the testis. Urol. Int. 42, 77-78.

Manikandan, R., Nathaniel, C., Reeve, N., Brough, R.J., 2006. Bilateral testicular metastases from prostatic carcinoma. Int. J. Urol. 13, 476-477.

Menon, S., Gujral, S., Bakshi, G., Tongaonkar, H.B., 2010. Bilateral testicular metastasis from prostatic adenocarcinoma mimicking an intertubular pattern of Seminoma and expressing. J. Cancer Res. Ther. 6, 97-99.

Patel, S.R., Richardson, R.L., Kvols, L., 1989. Metastatic cancer to the testes: a report of 20 cases and review of the literature. J. Urol. 142, 1003-1005.

Pienkos, E.A., Jablokow, K.R., 1972. Secondary testicular tumors. Cancer. 30, 481-485.

Richie, J.P., Steele, G.S., 2002. Neoplasms of the testis Campbell's. Urology, 8th. Philadelphia. 2876-2919.

Ulbright, T.M., Young, R.H., 2008. Metastatic carcinoma to the testis: A clinicopathologic analysis of 26 non incidental cases wit hemphasis on deceptive features. Am. J. Surg. Pathol. 32, 1683-1693.