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SPECT/CT findings of suspicious vertebral metastasis on planar bone scintigraphy

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ABSTRACT

Whole-body planar bone scintigraphy (WPBS) is a highly sensitive imaging method in the evaluation of bone lesions, but has a limited specificity. The aim of this study was to evaluate the contribution of SPECT/CT imaging method in the vertebral coloumn lesions which were interpreted as suspicious for metastasis on WPBS. A total of 56 patients who underwent SPECT/CT imaging due to the suspicious WPBS findings for metastasis on vertebral column were included in this retrospective study. Radiotracer accumulations on WPBS and SPECT/CT were determined. Based on the CT findings of SPECT/CT images, radiotracer accumulations were interpreted as benign/degenerative, malignant or suspicious for metastasis. Additional foci detected only with SPECT/CT were determined. A total of 121 foci were evaluated as suspicious for metastasis on WPBS. On SPECT/CT images, 67.8% of these foci were revealed with benign/degenerative lesions, 22.3% were evaluated as malign and 9.9% foci remained suspicious for metastasis. The number of benign/degenerative lesions was significantly higher than that of malign lesions. Pathological radiotracer accumulation was detected in extra 14 foci on the SPECT component of SPECT/CT. All of these foci were evaluated as benign/degenerative on fusion CT images. There was no statistically significant difference found between the total number of foci detected on WPBS and SPECT/CT. In conclusion, SPECT/CT was found to be able to identify a major part of the vertebral coloumn lesions which were interpreted as suspicious for metastasis and improve the diagnostic value of WPBS.

1. Introduction

Vertebral column is the most common site of metastatic lesions in the skeletal system (Disibio and French, 2008). Whole-body planar bone scintigraphy (WPBS) is a highly sensitive and noninvasive imaging method and has been widely used for the evaluation of bone lesions for a long time (Horger and Bares, 2006). In many studies, WPBS has been reported to have a high sensitivity in identifying bone metastases. However, specificity is limited and radiotracer accumulates in several benign conditions such as degenerative joint disease, inflammation, benign tumours and trauma (Rybak and Rosenthal, 2001). In a study, the specificity of WPBS for the characterization of isolated vertebral lesions was 36% (Sharma et al., 2013). Thus, degenerative pathologies are frequently observed in the joints of the vertebral column, localization of lesions is particularly important for differential diagnosis. Due to the low specificity of WPBS, additional diagnostic imaging techniques such as CT and MRI are often needed to characterize vertebral lesions.

Additional methods including single-photon emission computed tomography (SPECT) and SPECT/CT have been introduced to improve specificity of WPBS. SPECT imaging has increased the sensitivity and accuracy with higher lesion contrast and

crosssectional images (Ghosh, 2014). There are studies reporting that the localization of lesions could be determined with SPECT and thus the sensitivity could be increased relatively (Love et al., 2003). SPECT/CT, a fusion imaging method, combines high lesion contrast with SPECT and exact anatomical localization with CT which are very important factors for characterizing lesions (Kobayashi et al., 2005). The aim of this study was to evaluate the contribution of SPECT/CT imaging in vertebral lesions which were interpreted as suspicious for metastasis on WPBS.

2. Material and methods

A total of 56 patients with known malignancy who were referred to our center for WPBS between November 2017 and May 2019 were included in this retrospective study. According to the routine protocol of our center, additional SPECT/CT imaging had been applied to all patients because of suspicious findings for metastasis on vertebral column This retrospective study was conducted in accordance with the ethical principles outlined in the 1964 Helsinki Declaration.

For WPBS imaging, patients were injected 740-800 MBq Tc-99m MDP intravenously. Anterior and posterior whole-body planar images were obtained after 2-3 hours of radiotracer injection with either Siemens Symbia True Point SPECT/CT gamma camera or GE Discovery NM 630 dual head gamma camera. SPECT/CT imaging was performed with Siemens Symbia True Point SPECT/CT gamma camera. Immediately after planar images, SPECT imaging were acquired with 25 second/image parameters and CT imaging with 40-60 mass, 130 KeV and 5 mm thickness parameters. Planar and SPECT/CT images were analyzed visually in seperate sessions. The suspicious accumulations on vertebral column were determined on planar images. Radiotracer accumulations on the SPECT component of SPECT/CT images were interpreted as malignant, benign or suspicious for metastasis, based on findings of CT component. Presence of lytic, sclerotic, or mixed changes on CT images were suggested as malignant; osteophytes, spondylophytes, subchondral sclerosis or narrowing of the joint space were interpreted as benign/degenerative (Zhang et al., 2011). Lesions that did not meet the criteria for benign and malignant lesions were noted as suspicious for metastasis.

Pathological accumulations that were not observed on WPBS images but detected only with SPECT component of SPECT/CT were determined. SPECT/CT and WPBS findings were compared in terms of the number of total and suspicious lesions. The number and localization of benign/degenerative and malignant lesions observed on SPECT/CT were determined.

Distribution of variables was evaluated with Kolmogorov-Smirnov test. Chi-square test and Mann Whitney U test were used for categorical and continuous measurements respectively. The threshold value of 0.05 was accepted for statistical significance in all tests. Statistical analysis of the data was performed with SPSS 21.0 package program.

3. Results

A total of 56 patients (32 males, 24 females) were included in the study. Mean age was 63 years and age ranges were 26–87 years. Underlying malignant disease was prostate carcinoma in 24 patients, breast carcinoma in 16 patients, lung carcinoma in 12 patients, unknown primary carcinoma in 3 patients and bladder carcinoma in 1 patient.

On WPBS images, a total of 121 foci were evaluated as suspicious for metastasis in the vertebral column. On SPECT/CT images, 82 (67.8%) of these foci were revealed with benign/degenerative lesions, 27 (22.3%) were evaluated as malign lesions and 12 (9.9%) foci remained suspicious for metastasis.

The number of benign/degenerative lesions was significantly higher than that of malign lesions in the interpretation of SPECT/CT images ($p < 0.05$). Of the 82 lesions consistent with benign/degenerative changes, 41 (50.0%) were in the vertebral corpus, 19 (23.2%) in the intervertebral space, 15 (18.3%) in the facet joints, 4 (4.9%) in the spinous process and 3 (3.6%) in the costovertebral joint. WPBS and SPECT/CT images of a patient with degenerative changes in L2.-L3. vertebras were presented in Fig. 1.

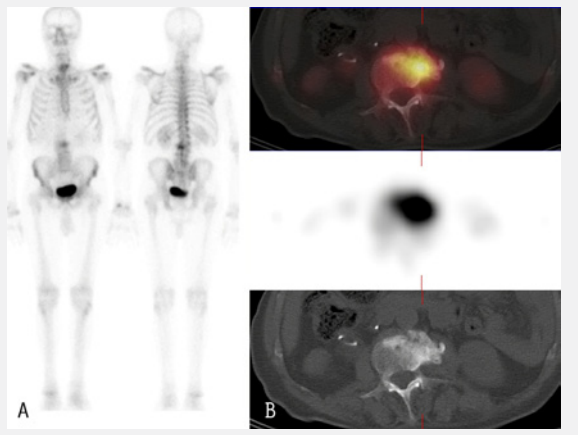

Fig. 1. Planar wholebody images of a 71-year-old male patient with prostate carcinoma showed osteoblastic activity in the left half of L2-L3 vertebra (A). CT images of SPECT-CT were revelaled with degenerative changes in the vertebral corpus and intervertebral space (B).

The localizations of foci evaluated as malign lesions were as follows: 23/27 (85.2%) were in the vertebral corpus, 2 (7.4%) were in the pedincule, 1 (3.7%) was in the costavertebral junction and 1 (3.7%) was in the spinous process. Fig. 2 represented images of a patient with metastasis in L2. vertebra.

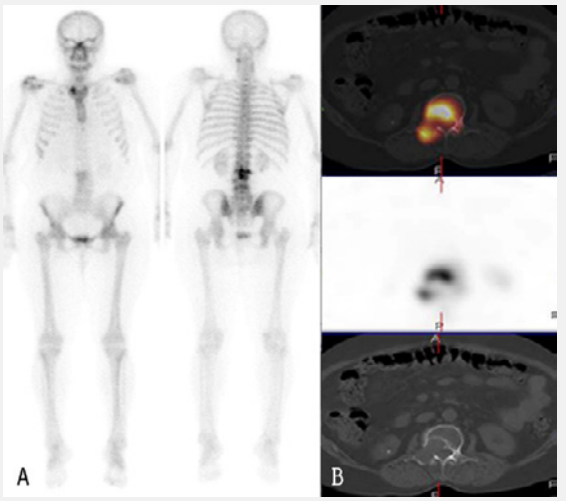

Fig. 2. Osteoblastic activity was detected in L2. vertebra on planar wholebody images of a 59-year-old woman with breast carcinoma (A). On SPECT-CT images, L2. There were destructive changes in the corpus with a soft tissue mass adjacent to the vertebra (B).

In a total of 12 foci, lesion characterization could not be made clearly and remained suspicious for metastasis; 4 foci in the vertebral corpus, 2 foci in the costavertebral joint, 3 foci in the spinous process and 3 foci in the facet joint. The localization of foci with benign/degenerative, malignant and suspicious findings were given in Table 1.

Table 1. SPECT/CT findings of vertebral coloumn lesions that were interpreted as suspicious for metastasis on whole body planar bone scintigraphy and extra benign/degenerative lesions detected only with SPECT/CT.

	SPECT/CT Imaging					
	Vertebral Corpus	**Pedin-cule**	**Inter-ver-tebral Space**	**Costa-vertebral Junction**	**Spinous Process**	**Facet Joint**
Malign	23	2	0	1	1	0
Benign/De-generative	41	0	19	3	4	15
Suspicious	4	0	0	2	3	3
Extra lesions (Benign/De-generative)	7	0	4	0	0	3

In addition to the 121 foci evaluated as suspicious on planar images, pathological radiotracer accumulation was detected in extra 14 foci on the SPECT component of SPECT/CT. All of these 14 foci were evaluated as benign/degenerative on fusion CT images; 7/14 were in the vertebral corpus, 4/14 were in the intervertebral space and 3/14 were in the facet joint. There was no statistically significant difference found between the total number of foci detected on WPBS and SPECT/CT. Images of a patient with additional benign/degenerative lesion in L5. vertebra on SPECT/CT images were presented in Fig. 3.

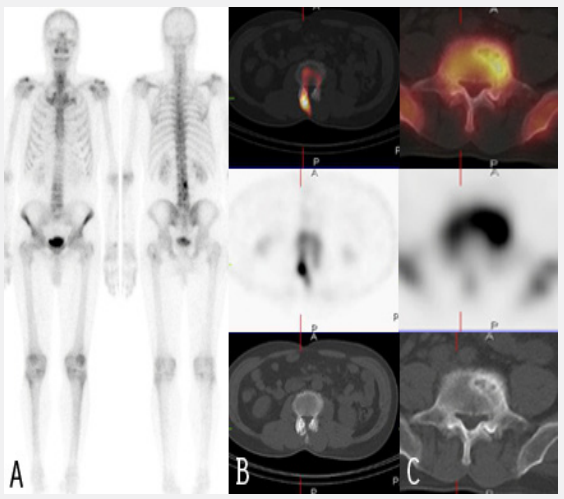

Fig. 3. A 62-year-old male patient with a history of prostate carcinoma had osteoblastic activity in the right half of the L3. vertebra on planar images (A). SPECT-CT images showed degenerative changes in the L3 vertebra facet joint (B). In addition, SPECT images showed an increased osteoblastic activity in the left half of the L5. vertebra corpus; CT findings were consistent with degenerative changes (C).

4. Discussion

Whole body planar bone scintigraphy has been the most widely used functional imaging modality to demonstrate metastatic bone lesions due to its widespread availability (Cuccurullo et al., 2013). Sclerotic bone metastasis can be distinguished very earlier on WPBS than on radiographs, because 5%-10% change in bone content is enough to detect a metastatic lesion on WPBS (Utsunomiya et al., 2006; Choi and Raghavan, 2012). Although the sensitivity of the technique is high, specificity is low because of some limitations and this makes the technic insufficient in the diagnostic procedure (O'Sullivan et al., 2015). Bone scintigraphy is nonspecific in the differential diagnosis of benign and malignant bone lesions and multipl degenerative and traumatic conditions accumulate radiotracer (Zhang et al., 2012). Morphological imaging methods are often required in addition to the WPBS to distinguish benign and metastatic lesions (Rajarubendra et al., 2010). SPECT/CT is a relatively new fusion imaging method that combines functional information by SPECT and morphological information by CT (Townsend, 2008). This retrospective study aimed to characterize vertebral coloumn lesions with SPECT/CT that were interpreted as suspicious for metastasis on WPBS.

The differential diagnosis of benign and malign bone lesions in patients with known malignancy is very important to determine treatment modality. In this study, 90.1% of the vertebral column lesions which were suspected for metastasis on WPBS, were exactly localized and characterized with SPECT/CT.

CT findings were consistent with benign/degenerative morphological changes in most of the vertebral column lesions (67.8%) which were generally localized at vertebral corpus and intervertebral space. It is important that, no additional imaging modality was needed for further evaluation of these patients.

Various techniques have been developed in order to increase the specificity of WPBS in the detection of metastatic lesions. As WPBS had limited value in localizing lesions due to the superimposition of bones, SPECT imaging provided better localisation with axial, coronal and sagittal slices. Some studies showed that, SPECT has a significant contribution to the specificity over WPBS (O'Sullivan et al., 2015). However, since there was no anatomic marker, SPECT method was still insufficient to determine the exact anatomical location (Reinartz et al., 2000). Increased sensitivity with SPECT imaging especially in vertebral column lesions was also reported (Savelli et al., 2001). However, no significant difference was found in this study between the number of detected lesions on WPBS and SPECT.

More specific bone scans were achieved with the introduction of SPECT/CT imaging in clinical practice (Horger et al., 2004; Jiang et al., 2013). In addition to the advantage of SPECT's cross-sectional images, CT component provided accurate localization and morphological evaluation of osteoblastic areas (Palmedo et al., 2014). Adusumilli et al. reported a 74.5% increase in definitive classification and a 26.6% reduction in the equivocal findings with SPECT/CT when compared to WPBS (Adusumilli et al., 2019). Vertebral column evaluation for metastatic foci on WPBS has some extra difficulties because of small bone structures with high degenerative tendency close to each other. In a study on vertebral coloumn lesions, SPECT/CT reduced equivocal results by 94.4% and the diagnostic accuracy was found significantly higher than SPECT (58.9% vs 91.1%). SPECT/CT imaging was known to have an important contribution in the evaluation of vertebral lesions, in terms of lesion characterization and localization (Zhang et al., 2011; Zhang et al., 2013). In this study, most of the lesions were characterized by SPECT/CT and the findings were similar to the literature. Another important finding of this study was that most of the vertebral column accumulations were located in areas consistent with benign/degenerative morphological changes on SPECT/CT. As histopathological findings or follow-up scans could not be obtained and this was a limitation of the study, the presence of small metastatic foci that may have developed on degenerative background could not be ruled out. However, study results based on the morphological changes observed on CT showed similar findings with literature based on histopathological findings. Further studies are needed with larger patient groups with histopathological diagnosis or long-term follow-up findings.

In conclusion, findings of this study showed that SPECT/CT is an important tool for the characterization of vertebral column lesions which are suspicious for metastasis on WPBS. In most of the patients, accumulations were compatible with benign/degenerative morphological changes observed on CT and elimination of further diagnostic imaging in these patients was an important advantage of SPECT/CT. It is thought that, SPECT/CT imaging which is currently available in a small number of center in our country should be used for the characterization of vertebral lesions.

REFERENCES

Adusumilli, P., Nejadhamzeeigilani, H., Pitts, K., McDermott, G., Scarsbrook, A.F., Vaidyanathan, S., Patel, C.N., Chowdhury, F.U., 2019. Protocol-driven multidetector SPECT/CT: Integration of hybrid imaging into the routine workflow of whole-body bone scintigraphy in oncology patients. Clin. Radiol. 75, 79.e1-79.e7.

Choi, J., Raghavan, M., 2012. Diagnostic imaging and image-guided therapy of skeletal metastases. Cancer Control. 19,102–112.

Cuccurullo, V., Cascini, G.L., Tamburrini, O., Rotondo, A., Mansi L., 2013. Bone metastases radiopharmaceuticals: An overview. Curr. Radiopharm. 6, 41–47.

Disibio, G., French, SW., 2008. Metastatic patterns of cancer: Results from a large autopsy study. Arch. Pathol. Lab. Med. 132, 931-939.

Ghosh, P., 2014. The role of SPECT/CT in skeletal malignancies. Semin. Musculoskelet. Radiol. 18, 175–193.

Horger, M., Eschmann, S.M., Pfannenberg, C., Vonthein, R., Besenfelder, H., Claussen, C.D., Bares, R., 2004. Evaluation of combined transmission and emission tomography for classification of skeletal lesions. Am. J. Roentgenol. 183, 655-661.

Horger. M., Bares, R., 2006. The role of single-photon emission computed tomography/computed tomography in benign and malignant bone disease. Semin. Nucl. Med. 36, 286-294.

Jiang, L., Han, L., Tan, H., Hu, P., Zhang, Y., Shi, H., 2013. Diagnostic value of 99mTc-MDP SPECT/spiral CT in assessing indeterminate spinal solitary lesion of patients without malignant history. Ann. Nucl. Med. 27, 460-467.

Kobayashi, K., Kusota, T., Nakai, T., Ushijima, Y., Nishimura, T., 2005. Do short-time SPECT images of bone scintigraphy improve the diagnostic value in the evaluation of solitary lesions in the thoracic spine in patients with extraskeletal malignancies? Ann. Nucl. Med. 19, 557-566.

Love, C., Din, A.S., Tomas, M.B., Kalapparambath, T.P., Palestro, C.J., 2003. Radionuclide bone imaging: An illustrative review. Radiographics. 23, 341-358.

O'Sullivan, G.J., Carty, F.L., Cronin, C.G., 2015. Imaging of bone metastasis: An update. World. J. Radiol. 28, 202–211.

Palmedo, H., Marx, C., Ebert, A., Kreft, B., Ko, Y., Turler, A., Vorreuther, R., Göhring, U., Schild, H.H., Gerhardt, T., Pöge, U., Ezziddin, S., Biersack, H.J., Ahmadzadehfar, H., 2014. Whole-body SPECT/CT for bone scintigraphy: Diagnostic value and effect on patient management in oncological patients. Eur. J. Nucl. Med. Mol. Imaging. 41, 59-67.

Rajarubendra, N., Bolton, D., Lawrentschuk, N., 2010. Diagnosis of bone metastases in urological malignancies-an update. Urology. 76, 782-790.

Reinartz, P., Schaffeldt, J., Sabri, O., Zimny, M., Nowak, B., Ostwald, E., Cremerius, U., Buell, U., 2000. Benign versus malignant osseous lesions in the lumbar vertebrae: Differentiation by means of bone SPET. Eur. J. Nucl. Med. 27, 721-726.

Rybak, L.D., Rosenthal, D.I., 2001. Radiological imaging for the diagnosis of bone metastases. Q. J. Nucl. Med. 45, 53-64.

Savelli, G., Maffioli, L., Maccauro, M., De Deckere, E., Bombardieri, E., 2001. Bone scintigraphy and the added value of SPECT (single photon emission tomography) in detecting skeletal lesions. Q. J. Nucl. Med. 45, 27-37.

Sharma, P., Dhull, V.S., Reddy, R.M., Bal, C., Thulkar, S., Malhotra, A., Kumar, R., 2013. Hybrid SPECT-CT for characterizing isolated vertebral lesions observed by bone scintigraphy: Comparison with planar scintigraphy, SPECT, and CT. Diagn. Interv. Radiol. 19, 33-40.

Townsend, D.W., 2008. Dual-modality imaging: Combining anatomy and function. J. Nucl. Med. 49, 938-955.

Utsunomiya, D., Shiraishi, S., Imuta, M., Tomiguchi, S., Kawanaka, K., Morishita, S., Awai, K., Yamashita, Y., 2006. Added value of SPECT/CT fusion in assessing suspected bone metastasis: Comparison with scintigraphy alone and nonfused scintigraphy and CT. Radiology. 238, 264-271.

Zhang, Y., Shi, H., Gu, Y., Xiu, Y., Li, B., Zhu, W., Chen, S., Yu, H., 2011. Differential diagnostic value of single-photon emission computed tomography/spiral computed tomography with Tc-99m-methylene diphosphonate in patients with spinal lesions. Nucl. Med. Commun. 32, 1194– 1200.

Zhang, Y., Zhao, C., Liu, H., Hou, H., Zhang, H., 2012. Multiple metastasis-like bone lesions in scintigraphic imaging. J. Biomed. Biotechnol. 957364.

Zhang, Y., Shi, H., Cheng, D., Jiang, L., Xiu, Y., Li, B., Gu, Y., Chen, S., 2013. Added value of SPECT/spiral CT versus SPECT in diagnosing solitary spinal lesions in patients with extraskeletal malignancies. Nucl. Med. Commun. 34, 451-458.

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Outcomes of low-profile plate-screw osteosynthesis in unstable extra-articular fractures of the proximal phalanx

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ABSTRACT

In this study, we aimed to present radiologic and functional outcomes of extra articular proximal phalangeal fractures treated with low profile plate and screw osteosynthesis. The study included 20 patients who had undergone osteosynthesis with low profile plate and non-locking screws due to extra-articular closed proximal phalangeal instable fractures. Clinical and radiologic data were evaluated retrospectively. Postoperative 6th month follow up data were obtained and statistically analyzed. Active and passive range of motion of the metacarpophalangeal and interphalangeal joint; total active motion grip strength of injured and uninjured visual analog scale for pain DASH score have been evaluated, distance between pulpa and palmar curve is measured. Belsky score, presence of reoperation and complications were noted. The mean time to radiologic union was 4.2 (3-6) weeks. Functional evaluation of the patients revealed a mean MCF flexion of 87.3 (75-90), a mean PIP flexion of 94.3 (65-100), mean DIP flexion of 77.6 (75-80), mean total active motion of 259 (210-270) degrees. Grip strength in the injured hand was 52.7 (40-58) kgw, and in the uninjured hand it was 54.4 (42-60) kgw. There was no statistically significant difference in grip strenght ($p<0.05$). The mean visual analogue scale score was 0.8 (0-2). The mean DASH score was 7 (2-27) and the mean distance between pulpa and palmar curve was 3 (0-8) mm. Open reduction and low-profile plate and screw fixation of proximal phalangeal fracture in treatment of unstable extra-articular fractures of the proximal phalanx with early rehabilitation yields satisfactory functional and radiologic outcomes.

1. Introduction

Proximal phalangeal fractures are common finger fractures (Drenth and Klasen, 1998). Fracture type, stability and sustainability of the fracture are major determinants in the treatment (Le Nen, 2014). In proximal phalangeal fractures, the fracture fragments are acted on by deforming forces of the interosseous muscles, flexors and extensors. The effects of deforming forces on the fracture fragments result in stable (transverse) and unstable (spiral, oblique, and fragmented) fractures (Kurzen et al., 2006). Stable fractures are usually treated by conservative methods. Ensuring periosteal continuity contributes to stability of these fractures. However, it is essential to provide anatomic reduction and maintain stabilization in unstable fractures (Lins et al., 1996; Kurzen et al., 2006).

The main objective is to enable early mobilization and union through stable and rigid fixation (Robinson et al., 2017). Closed reduction, Kirschner (K)-wire fixation, screw fixation, intramedullary screw fixation, external fixation, open reduction, and plate–screw fixation are commonly used methods in surgical treatment (Kozin et al., 2000; Kamath et al., 2011; Faruqui et al., 2012; Franz et al., 2012; Gaston and Chadderdon, 2012).

However, advantages and disadvantages have been reported for each method and there is still debate over optimal surgical treatment of extra-articular proximal phalangeal fractures (Ebinger et al., 1999; Lee and Jupiter, 2000; Gaston and Chadderdon, 2012; Desaldeleer-Le Sant et al., 2017). In this study, we aimed to discuss radiological and clinical results of plate–screw fixation, which we performed in 20 cases with extra-articular unstable fracture of the proximal phalanx.

2. Material and method

We retrospectively reviewed the clinical and radiological data of 20 patients, who underwent open reduction and low-profile fixation (ORIF) using a 1.5-mm titanium mini-plate and non-locking screws for closed, unstable, extra-articular fractures of the proximal phalanx. Informed consent was obtained from all patients preoperatively. Approval was granted by the institutional review board. Patients, who underwent closed reduction for closed, extra-articular, unstable (spiral, long oblique, and comminuted) fractures and patients, those who underwent ORIF for transverse fractures for which an acceptable reduction and stability was not achieved, and those who were followed up for a minimum of 6 months were included in the study. Patients with ipsilateral fractures, open fractures, intra-articular fractures, thumb fractures, and pathological fractures and those with an open epiphysis were excluded from the study. The Local Ethics Committee approved the study (Erzurum BEAH KAEK Ethical Committee (19/02/2018, No: 2018/04–23)).

Fracture types were classified according to the AO fracture classification system (Lee and Jupiter, 2000). Evaluations and statistical analyses were performed on the basis of the evaluated parameters at 6 months after surgery. The active and passive metacarpophalangeal (MP) joint range of motion (ROM), interphalangeal (IP) joint ROM, total active motion (TAM), grip strength (kgW) in the affected and unaffected hands (SAEHAN Hydraulic Hand Dynamometer [SH5001], Gyeongnam, South Korea), visual analog scale (VAS) score, DASH score (Hudak et al., 1996), the distance between the pulp and palmar crease in the operated finger (mm), the Belsky score (Belsky et al., 1984), reoperation status and complications were evaluated. Bone union, angulation and shortness evaluations were made with posteroanterior, lateral and 30°- 45° pronation and/or supine oblique radiographs taken at 1st, 2nd, 3rd and 6th month after surgery. The evaluation was performed by other surgeons who contributed to the study other than the operating surgeon.

Surgical method and postoperative protocol

All of the patients were operated by a single surgeon. All patients were operated in the supine position, under infraclavicular block anesthesia and with tourniquet application. A longitudinal incision was made on the dorsal aspect of the finger with the forearm in full pronation. The extensor tendon is split longitudinally for exposure. The periosteum was similarly dissected to sufficiently expose the fracture line for subsequent plate–screw fixation. The fractured ends were cleaned and anatomic reduction was achieved with a reduction clamp while preventing interposition of soft tissues. A low-profile 1.5-mm titanium mini-plate (TriMed®, Phalanx plate, Ankara, Turkey) was placed dorsally. A minimum of two screws were placed on each side of the fracture line in a way that at least four cortices would be passed through. We first placed interfragmentary screws in the long oblique or spiral fractures appropriate for interfragmentary screw fixation. We then performed plate–screw fixation. Anatomical and rotational alignment and angulation were confirmed under fluoroscopic guidance. After ORIF, we performed meticulous periosteal and extensor tendon repair (Figs. 1A-D). After surgery, all patients were kept in short-arm splints up to the proximal IP joint until edema and pain resolved. After the first week, passive exercises were initiated. After the second week, the splint was only used at night with an intention of early MP joint mobilization. Night splinting was terminated after the fourth week, and active motion was allowed. At the end of the sixth week, intense daily activities were allowed.

Fig. 1. A–D. Plate application to the 3rd proximal phalanx fracture in the right hand of a 43-year-old male patient (A), periosteal repair (B) and image of the completed repair (C), periosteal repair and image of the completed repair of the tendon (D).

3. Results

Nineteen patients were male and one patient was female. The mean age was 38.9 (19–61) years. Nine patients had fracture in the right hand, whereas 11 patients had fracture in the left hand. All patients were right-handed. Five patients had a fracture in the 2nd phalanx, 4 patients in the 3rd phalanx, 5 patients in the 4th phalanx and six patients in the 5th phalanx. When the etiology of the fracture was examined, the cause of fracture was blow by a heavy object in three patients, falls in 11 patients, slamming the hand in a door in two patients, road traffic accident involving passengers in three patients and work accident in one patient. Ten patients had diaphyseal (shaft) fracture and 10 patients had proximal metaphyseal fracture. The fracture pattern was comminuted fracture in eight patients, spiral-oblique in six patients and unstable transverse fracture in six patients. The mean time from admission of the patients to the hospital to surgery was 33 (8–72)h. Eleven patients were smokers and nine patients were nonsmokers. We performed splint immobilization for 7 days after surgery. All demographic data of the patients are presented in Table 1.

Table 1. Demographic Data of Patients (R: Right, L: Left, M: Male, F: Female)

PATIENT	AGE	SIDE	FRACTURED PHALANX	GENDER	TRAUMA TYPE	OCCUPATION	AO FRACTURE TYPE	FRACTURE PATTERN	TIME UNTIL OPERATION	IMPLANT REMOVAL	SMOKING STATUS
1	43	R	3	M	Blow by heavy object	Worker	Shaft	Fragmented	48	No	No
2	54	L	2	M	Fall	Retired	Proximal metaphysis	Long oblique	72	No	Yes
3	35	R	2	M	Fall	Worker	Proximal metaphysis	Long oblique	24	No	Yes
4	26	L	3	F	Fall	Student	Shaft	Fragmented	24	No	No
5	21	L	5	M	Fall	Student	Shaft	Fragmented	48	No	Yes
6	61	R	4	M	Thresher machine	Farmer	Shaft	Fragmented	8	Yes	Yes
7	54	L	2	M	Fall	Retired	Proximal Metaphysis	Transvers	12	No	No
8	19	L	5	M	Slamming in a door	Asker	Distal Metaphysis	Long oblique	72	No	Yes
9	39	R	5	M	Blow by heavy object	Worker	Proximal Metaphysis	Long oblique	48	No	No
10	33	L	4	M	Fall	Farmer	Shaft	Fragmented	12	No	No
11	40	R	3	M	Fall	Worker	Proximal metaphysis	Transvers	48	No	Yes
12	37	L	4	M	Road traffic accident as a passenger/driver	Worker	Shaft	Fragmented	24	No	Yes
13	42	R	2	M	Road traffic accident as a passenger/driver	Farmer	Shaft	Transvers	12	No	Yes
14	21	L	5	M	Fall	Student	Shaft	Fragmented	48	No	Yes
15	61	R	4	M	Road traffic accident as a passenger/driver	Farmer	Shaft	Fragmented	8	No	Yes
16	54	L	2	M	Fall	Retired	Proximal metaphysis	Transvers	12	No	No
17	19	L	5	M	Slamming in a door	Asker	Distal metaphysis	Long oblique	72	No	Yes
18	39	R	5	M	Blow by heavy object	Worker	Proximal metaphysis	Long oblique	48	No	No
19	33	L	4	M	Fall	Farmer	Shaft	Fragmented	12	No	No
20	46	R	3	M	Falls	Retired	Proximal metaphysis	Transvers	12	No	No

All patients were followed up for a mean duration of 16 (6–30) months. Radiological union was achieved in a mean duration of 4.2 (3–6) weeks (Figs. 2A-H). When functional results of the patients were evaluated, the mean MP joint flexion was 87.3° (75°–90°), the mean proximal IP joint flexion was 94.3° (65°–100°), the mean distal IP joint flexion was 77.6° (75°–80°), and the mean TAM was 259° (210°–270°). The mean passive MP joint flexion was 87.5° (85°–90°), the mean proximal IP joint flexion was 95.8° (90°–100°) and the mean distal IP joint flexion was 78.3° (75°–80°). Grip strength in the fractured hand was 52.7 (40–58) kgW, whereas it was 54.4 (42–60) kgW in the intact hand. There was no statistically significant difference in terms of grip strength ($p<0.05$). The mean VAS score was 0.8 (0–2), the mean DASH score was 7 (2–27), the mean distance between the finger pulp and palmar curve was 3 (0–8) mm. The Belsky score was excellent in 12 patients, good in seven patients, and poor in one patient (Table 2). We performed tenolysis in one patient for flexion contracture. Implant removal was also performed in the same patient. Sudeck's atrophy was observed in the same patient which lasted for approximately 4 weeks. We achieved improvement with physical therapy, contrast bath therapy and pharmacological treatment. There were no complications such as nonunion, late union, superficial or deep infection and tenosynovitis. There were no patients in whom implant removal was performed, with the exception of patient who underwent tenolysis. No patients developed soft-tissue and skin irritation. Displacement, angulation or rotational deformity were not observed radiologically in any patient.

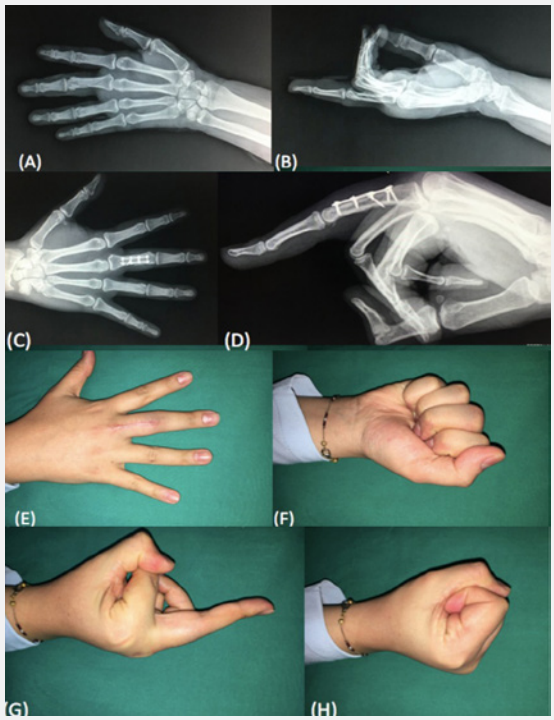

Fig. 2. A-H. Plain anteroposterior radiograph of the 3rd proximal phalanx shaft, spiral fragmented fracture due to a fall on the left hand (A), lateral radiograph (B), postoperative 6th month anteroposterior direct radiograph (C), plain lateral radiograph (D), images demonstrating functional joint movements; dorsal incision scar, extension of the finger and the hand (E), volar fist position (F), isolated 3rd finger extension (G) and image of the lateral fist position of the hand (H).

Table 2. Functional and Radiological Results of Patients (MP: Metacarpophalangeal, IP: Interphalangeal, VAS: Visual analog scale, DASH: Disabilities of the arm, shoulder, and hand score)

PATIENT	MP JOINT ACTIVE/ PASSIVE FLEXION (°)	PROXIMAL IP JOINT ACTIVE/ PASSIVE FLEXION (°)	DISTAL IP JOINT ACTIVE/ PASSIVE FLEXION (°)	TOTAL ACTIVE RANGE OF MOTION (°)	FRACTURED HAND GRIP STRENGTH (kgw)	HEALTHY HAND GRIP STRENGTH (kgw)	VAS	DASH	DISTANCE BETWEEN FINGER PULP AND FINGER CURVE	BELSKY SCORE	FOLLOW-UP PERIOD (WEEK)	UNION PERIOD (WEEK)	REOPERATION
1	85/85	90/90	75/75	250	57	59	1	9.09	3	Good	6	3	No
2	85/85	95/95	78/78	258	46	45	1	4.54	3	Good	9	4	No
3	90/90	100/100	80/80	270	44	46	0	4.54	0	Excellent	12	4	No
4	85/85	95/95	76/76	256	40	42	1	6.81	2	Good	12	4	No
5	90/90	95/95	80/80	265	53	56	1	4.54	2	Excellent	24	5	No
6	75/85	65/90	70/78	210	46	54	2	27.27	8	Poor	16	6	No
7	90/90	100/100	80/80	270	54	55	1	4.54	0	Excellent	14	4	No
8	85/85	95/95	76/76	256	58	59	1	9.09	3	Good	20	3	No
9	85/85	95/95	75/75	254	57	59	1	6.81	4	Excellent	12	4	No
10	90/90	100/100	80/80	270	55	54	0	4.54	0	Excellent	12	4	No

11	90/90	100/100	80/80	270	52	53	0	2.27	0	Excellent	12	4	No
12	85/85	90/90	76/76	251	58	60	0	4.54	4	Good	22	4	No
13	85/85	90/90	75/80	250	48	48	1	6.81	5	Good	30	5	No
14	90/90	95/95	80/80	265	53	56	1	4.54	2	Excellent	14	4	No
15	95/90	90/95	80/80	265	55	60	1	4.54	8	Excellent	16	5	No
16	90/90	100/100	80/80	270	54	55	1	4.54	0	Excellent	12	4	No
17	85/85	95/95	76/76	256	58	59	1	9.09	3	Good	18	5	No
18	85/85	95/95	75/76	254	57	59	1	6.81	4	Excellent	18	4	No
19	90/90	100/100	80/80	270	55	54	0	4.54	0	Excellent	22	4	No
20	90/90	100/100	80/80	270	54	55	1	4.54	0	Excellent	12	4	No

Statistical methods

SPSS software package was used in the analysis of the data. The data were presented as number, percentage, mean and standard deviation. Variables included in the analysis were tested whether they showed normal distribution using the Kolmogorov–Smirnov Test. Spearman's correlation analysis was used to evaluate the correlation between the parameters. The correlation between the handgrip strength in the fractured hand and in the intact was evaluated using the Mann–Whitney U-test. The correlation between the grip strength in the treated hand, MP joint flexion and IP joint flexion was assessed by the Spearman's correlation analysis. The level of significance was set to $p<0.05$.

4. Discussion

Proximal phalangeal fractures are common orthopedic injuries (Lee and Jupiter, 2000; Lögters et al., 2017). The first step that is recommended in the management is to evaluate stability of the fracture (Rajesh et al., 2007). Positive results can be obtained in stable fractures through conservative treatment methods (short-arm splint application, buddy taping) (Lins et al., 1996; Kozin et al., 2000; Held et al., 2013). It was reported that a finger that has undergone a trauma might develop more stiffness than a finger that has undergone surgery (von Kieseritzky et al., 2017). For this reason, early motion cannot be achieved by conservative methods that will be applied independently of the stability of the fracture. In addition, conservative methods that are applied in unstable fractures can lead to functional losses to a great extent (Desaldeleer-Le Sant et al., 2017). At this stage, surgical treatment should be planned depending on fracture site and type. The main objective is to perform fixation using an anatomic and sustainable fixation method so as to avoid shortening and rotational deformity that may occur in comminuted, long spiral-oblique fractures (Henry, 2008). Rigid fixation should be applied to obtain a functional hand and to allow early motion (Kamath et al., 2011; Le Nen, 2014; Robinson et al., 2017).

The optimal surgical treatment of proximal phalangeal fractures remains controversial. Treatment recommendations have been made depending on the localization of fracture in the bone and type of fracture. K-wire or screw fixation have been recommended in intra-articular base fractures; K-wire fixation has been recommended in extra-articular transverse fractures of the phalangeal base; K-wire, screw or plate fixation have been recommended in transverse or short oblique fractures; K-wire or screw fixation has been recommended in spiral or long oblique fractures, multiple K-wire or plate fixation has been recommended in partial diaphyseal fractures, and K-wire or screw fixation has been recommended in condylar fractures. There are limited number of studies comparing different treatment methods in proximal phalangeal fractures. Advantages and disadvantages of different fixation methods have been reported. One of the major advantages of plate and screw fixation is providing sooner rehabilitation resulting in better functional outcomes (Meals and Meals, 2013; Le Nen, 2014; Li et al., 2015; Desaldeleer-Le Sant et al., 2017). In this study, unstable, extra-articular proximal phalangeal fractures were operated using low-profile titanium plates and as per AO guidelines (Lee and Jupiter, 2000). Adequate stability was achieved in all patients and early motion was initiated. It was ensured that all patients returned to their preoperative activities. Displacement, angulation and rotational deformity did not develop in any patient. There are studies suggesting that dorsal approach is a risk factor for tendon adhesion, because of which dorsolateral approach should be preferred. Depending on the surgical treatment method employed and mobilization in proximal phalangeal fractures, extensor tendon adhesions and joint stiffness

may lead to poor functional outcomes and this may sometimes necessitate implant removal (Page and Stern, 1998; Li et al., 2015; Onishi et al., 2015; Desaldeleer-Le Sant et al., 2017). We believe that, careful handling of soft tissues and meticulous periosteal repair during surgery decrease adhesions. None of the patients, except the one patient that underwent tenolysis, required implant removal.

Malunion is the most common osseous complication after treatment of proximal phalangeal fractures, but nonunion, arthritis, and infections can also be observed (Başar et al., 2015; Desaldeleer-Le Sant et al., 2017). In this study, radiological union was achieved in a mean duration of 4.2 (3–6) weeks. Studies in the literature reported that union occurs in a mean duration of 4–8 weeks (Horton et al., 2003; Desaldeleer-Le Sant et al., 2017). Better functional outcomes and recovery are achieved in patients treated with rigid fixation methods that allow early postoperative rehabilitation (Desaldeleer-Le Sant et al., 2017). In the study, there was no patient that developed adhesions and had poor functional outcomes except one patient who underwent tenolysis. In the comparison of grip strength, there was no statistically significant difference between the affected hand and unaffected hand ($p<0.05$). Functional evaluation parameters [VAS 0.8 (0-2), DASH 7 (2-27), finger pulp and finger curve distance 3 (0-8) mm] were similar to the comparative studies in the literature (Li et al., 2015; Desaldeleer-Le Sant et al., 2017). The Belsky score was excellent in 12 patients, good in seven patients, and poor in one patient. Cold intolerance and Sudeck's atrophy are among rare complications that may occur. Although the duration of immobilization was similar among patients, there was no patient that developed Sudeck's atrophy other than the patient who underwent tenolysis.

Retrospective study design, inclusion of patients that underwent fixation using a single fixation material and heterogeneous distribution of fractures were the limitations of the study. The operations in the present study were performed by a single surgeon; however, postoperative evaluations were performed by different surgeons in order to avoid bias in the postoperative evaluation. In this context, there is a need for multicenter, prospective and controlled studies on homogeneous fracture patterns using different fixation materials.

The treatment of extra-articular proximal phalangeal fractures should allow restoring functional status. In selected patients with appropriate indications (unstable transverse, comminuted, and long spiral-oblique fractures), dorsal approach provides sufficient exposure and anatomical and rigid fixation can be achieved. Meticulous periosteal repair minimizes adhesion and prevents contracture. Rigid fixation allows early motion while accelerating soft-tissue healing and bone union (Lögters et al., 2017). In treatment of extra-articular and unstable fractures of the proximal phalanx successful radiological and functional outcomes can be obtained with open reduction, a low-profile plate–screw fixation and early rehabilitation.

REFERENCES

Başar, H., Başar, B., Başçı, O., Topkar, O. M., Erol, B., Tetik, C., 2015. Comparison of treatment of oblique and spiral metacarpal and phalangeal fractures with mini plate plus screw or screw only. Arch. Orthop. Trauma. Surg. 135, 499-504.

Belsky, M. R., Eaton, R. G., Lane, L. B., 1984. Closed reduction and internal fixation of proximal phalangeal fractures. J. Hand Surg. Am. 9, 725-729.

Desaldeleer-Le Sant, A. S., Le Sant, A., Beauthier-Landauer, V., Kerfant, N., Le Nen, D., 2017. Surgical management of closed, isolated proximal phalanx fractures in the long fingers: Functional outcomes and complications of 87 fractures. Hand Surg. Rehabil. 36, 127-135.

Drenth, D., and Klasen, H., 1998. External fixation for phalangeal and metacarpal fractures. J. Bone Joint. Surg. Br. 80, 227-230.

Ebinger, T., Erhard, N., Kinzl, L., Mentzel, M., 1999. Dynamic treatment of displaced proximal phalangeal fractures. J. Hand Surg. 24, 1254-1262.

Faruqui, S., Stern, P. J., Kiefhaber, T. R., 2012. Percutaneous pinning of fractures in the proximal third of the proximal phalanx: Complications and outcomes. J. Hand Surg. 37, 1342-1348.

Franz, T., Von Wartburg, U., Schibli-Beer, S., Jung, F., Jandali, A., Calcagni, M., Hug, U., 2012. Extra-articular fractures of the proximal phalanges of the fingers: A comparison of 2 methods of functional, conservative treatment. J. Hand Surg. 37, 889-898.

Gaston, R. G., Chadderdon, C., 2012. Phalangeal fractures: Displaced/nondisplaced. Hand Clin. 28, 395-401.

Held, M., Jordaan, P., Laubscher, M., Singer, M., Solomons, M., 2013. Conservative treatment of fractures of the proximal phalanx: An option even for unstable fracture patterns. Hand Surg. 18, 229-234.

Henry, M. H., 2008. Fractures of the proximal phalanx and metacarpals in the hand: Preferred methods of stabilization. JAAOS. 16, 586-595.

Horton, T., Hatton, M., Davis, T., 2003. A prospective randomized controlled study of fixation of long oblique and spiral shaft fractures of the proximal phalanx: Closed reduction and percutaneous Kirschner wiring versus open reduction and lag screw fixation. J. Hand Surg. 28, 5-9.

Hudak, P. L., Amadio, P. C., Bombardier, C., Beaton, D., Cole, D., Davis, A., Marx, R. G., 1996. Development of an upper extremity outcome measure: The DASH (Disabilities of the Arm, Shoulder, and Hand). Am. J. Ind. Med. 29, 602-608.

Kamath, J. B., Harshvardhan, D. M. N., Bansal, A., 2011. Current concepts in managing fractures of metacarpal and phalangess. Indian J. Plast. Surg. Assoc. Plastic. Surg. India. 44, 2, 203.

Kozin, S. H., Thoder, J. J., Lieberman, G., 2000. Operative treatment of metacarpal and phalangeal shaft fractures. JAAOS. 8, 111-121.

Kurzen, P., Fusetti, C., Bonaccio, M., Nagy, L., 2006. Complications after plate fixation of phalangeal fractures. J. Trauma. 60, 841-843.

Le Nen, D., 2014. Extra-articular fractures of the digital metacarpals and phalanges of the long fingers. Chir. Main. 33, 1-12.

Lee, S. G., Jupiter, J. B., 2000. Phalangeal and metacarpal fractures of the hand. Hand Clin. 16, 323-332, vii.

Li, G., Liu, S., Chen, G., Li, Z., Liu, Y., Sun, G., Guan, M., 2015. Comparison of clinical outcomes of phalangeal fracture treated with dorsolateral approach or post-middle approach using ao mini titanium plate. Indian J. Surg. 77, 657-661.

Lins, R. E., Myers, B. S., Spinner, R. J., Levin, L. S., 1996. A comparative mechanical analysis of plate fixation in a proximal phalangeal fracture model. J. Hand Surg. 21, 1059-1064.

Lögters, T. T., Lee, H. H., Gehrmann, S., Windolf, J., Kaufmann, R. A., 2017. Proximal phalanx fracture management. Hand. 13, 376-383.

Meals, C., Meals, R., 2013. Hand fractures: A review of current treatment strategies. J. Hand Surg. 38, 1021-1031.

Onishi, T., Omokawa, S., Shimizu, T., Fujitani, R., Shigematsu, K., Tanaka, Y., 2015. Predictors of postoperative finger stiffness in unstable proximal phalangeal fractures. Plast. Reconstr. Surg. Glob. Open. 3, e431.

Page, S. M., Stern, P. J., 1998. Complications and range of motion following plate fixation of metacarpal and phalangeal fractures. J. Hand Surg. 23, 827-832.

Rajesh, G., Ip, W., Chow, S., Fung, B., 2007. Dynamic treatment for proximal phalangeal fracture of the hand. J. Orthop. Surg. 15, 211-215.

Robinson, L. P., Gaspar, M. P., Strohl, A. B., Teplitsky, S. L., Gandhi, S. D., Kane, P. M., Osterman, A. L., 2017. Dorsal versus lateral plate fixation of finger proximal phalangeal fractures: A retrospective study. Arch. Orthop. Trauma. Surg. 137, 567-572.

von Kieseritzky, J., Nordström, J., Arner, M., 2017. Reoperations and postoperative complications after osteosynthesis of phalangeal fractures: A retrospective cohort study. J. Plastic. Surg. Hand Surg. 51, 458-462.

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Importance of atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H)

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ABSTRACT

In this study, we evaluated the biopsy counterparts of atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H) cases. This was a cross-sectional, retrospective study on ASC-H cases. The follow-up results of ASC-H cases diagnosed during routine primary screening between 2011 and 2018 were evaluated, and the relationship between clinicopathological parameters, high risk Human Papilloma Virus (hrHPV) test and patients' ages at diagnosis were evaluated. Among one hundred sixty-nine ASC-H patients, high grade squamous intraepithelial lesion (HSIL) was detected in 56 (33.1%), low grade squamous intraepithelial lesion (LSIL) in 59 (35%), squamous cell carcinoma in 5 (3%) and adenocarcinoma in 1 (0.5%). HPV 16 was detected in 41 (24.4%) cases and HPV 18 in 26 (16%) cases, and 51 patients had low risk of HPV (lrHPV). The mean age of the patients with hrHPV was 31.78 ± 8.22, and the mean age of the patients with lrHPV was 34.77 ± 5.47. HPV positivity in ASC-H smears was significantly correlated with age ($p = 0.004$). General linear regression analysis showed that biopsy results were significantly correlated with HPV in high-risk patients compared to low-risk patients. hrHPV evaluation in ASC-H follow-up is significant for cervical premalignant lesion. A management strategy that requires close monitoring in women with ASCH and under 40 years old, especially in association with hrHPV, should be considered.

1. Introduction

Cervical cancer is an important global health issue: it is the third most common cancer in women worldwide and the second among women aged 15-44 years, with over 529.000 cases of cervical cancer diagnosed every year worldwide (De Sanjose S, 2012). Cervical cancer was responsible for 2.7 million age-weighted years of life lost (YLL) in 2000 (Forman, 2012). Fortunately, thanks to the widespread use of the PapSmear Test (PST) screening method, the incidence has been reduced considerably (Waxman, 2005). However, although PST is useful for cancer screening, it has high false-negative

rates and limitations such as interobserver variability. The presence of atypical cells in smears is one of the most important diagnostic problems for cervical cancer screening (Papanicolaou and Traut, 1997).

In the first Bethesda System described in 1988, "atypical squamous cells of undetermined significance" were identified (Koss, 1989). According to the 2001 Bethesda system, atypical squamous cells (ASC) were divided into two groups: Atypical Squamous Cells of Undetermined Significance (ASC-US) and Atypical Squamous Cells cannot exclude High-grade squamous intraepithelial lesion (ASC-H) (Apgar et al., 2003). ASC-H represents 5-10% of ASC diagnoses and accounts for approximately 0.2% of cytological interpretations (Apgar et al., 2003). The ASC-H category includes ASCs that exhibit characteristics equivalent to the idea of a high-grade squamous intraepithelial lesion (HSIL), but are not sufficient to diagnoss. The probability of having Cervical Intraepithelial Neoplasia-2 (CIN 2) or Cervical Intraepithelial Neoplasia-3 (CIN 3) approved by biopsy for a woman with cervical cytology result interpreted as ASCs are 5-17%, and the underlying HSIL rates in ASC-H patients range from 24% to 94% (Galliano et al., 2011; Gilani et al., 2014).

Recently, it has been shown that ASC-H is not a homogeneous category and has a broad spectrum of cyto-morphological patterns associated with different clinicopathological categories classified by biopsy and Human Papilloma Virus (HPV) test results (Solomon et al., 2002). HPV positivity rates vary between 70-86% in patients with this diagnosis (Solomon et al., 2002). Initial examination of patients diagnosed with ASC-H is recommended as colposcopy since HSIL and higher-grade lesions are more likely to be present (Massad et al., 2013). If no lesion can be shown on colposcopy, Colposcopic - histological - cytological examinations should be reviewed (Massad et al., 2013).

This study investigated the cytology and biopsy results of 169 ASC-H cases identified during routine primary screening, and analyzed abnormal biopsy results, especially in ASC-H cases with a positive test for hrHPV.

2. Materials and methods

The study was conducted in the Oncology Center of the Health Sciences University, Tepecik Training and Research Hospital, which provides tertiary and basic health care services for patients through many health centers. The Local Ethics Committee approved the study (University of Health Sciences, Tepecik Education and Research Hospital Ethical Committee (26/07/2018, No: 2018/9–6). The universal principles of the Helsinki Declaration were applied. In this study, we evaluated the biopsy results of 169 patients diagnosed with ASC-H between January 2010 and September 2018. Age (25-40 years), socioeconomic level (<500, 500-1000, or >1000 dollars per month), educational status (primary, secondary, high school, university), smoking status (smoker or non-smoker), parity, first sexual intercourse age (16-29) and body mass index (BMI) were recorded. Patients were divided into two groups according to the presence of HSIL and hrHPV separately. Demographic parameters were compared in HSIL and non HSIL groups. Patient ages and pathological findings were compared according to HPV risk groups.

Pregnant patients, patients in menopause, those who had a hysterectomy history as well as under hormone replacement therapy, those who had multiple HPV DNA types and those with a history of HPV vaccine were excluded. Patients who could not have satisfactory colposcopic examination or insufficient and/or absent biopsy were also excluded from the study.

Since 2014, women's participation in the HPV DNA screening program across the country has been provided by the KETEM (Cancer Early Diagnosis Screening and Training Center) affiliated with the Ministry of Health (Gultekin et al., 2018). Screening was performed by primary health care personnel at KETEM (family physicians and general practitioners trained in this field). Hybrid Capture 2 kits (Qiagen, Hilden, Germany) were sent to the KETEM screening center by the central laboratory of the Ministry of Health to collect HPV DNA samples. Two samples were taken from each woman participating in the screening, one for traditional cytology test and the other for the HPV DNA test. Cytology test results based on the 2001 Bethesda classification were reported by four pathologists in the central laboratory of the Ministry of Health. The second sample, which was obtained for HPV, was taken with a separate brush and placed in 5 mL of standard transport medium from the Hybrid Capture 2 collection kit for HPV DNA testing. Genotyping was performed using the CLART HPV kit (Genomica, Madrid, Spain) for any patient with a non-specific HPV test result (Gultekin et al., 2018). HPV genotype results were evaluated in the central laboratory of the Ministry of Health, and the results were delivered to recipients online using a fully automated operating system. HPV types 16, 18, 31, 33, 45, 51, 58, 59 and 68 were considered high-risk, 53 and 66 probable high-risk and 6, 11, 40, 54 and 70 were considered low-risk for etiopathogenesis of cervical cancer (Milutin et al., 2008).

All patients underwent colposcopic observation by experienced colposcopists with a binocular colposcope (Colposcope 1D-21100, Leisegang GmbH, 2014-03, Germany) with a green filter capable of 4.5 to 30 magnifications. Cervix was first washed with saline, then scanned at a small magnification, and vascularization pathologies were investigated with a green filter. Then, 3% acetic acid was applied and left for at least 60 seconds, and then the cervix was re-screened at small (x10) and large (x40) magnifications. After the location

of the aceto-white areas and vascular pathologies, Lugol solution was applied. After staining with cervix with lugol solution, iodine-free areas were determined, and cervical biopsy was performed with forceps from iodine-free areas and aceto-white, mosaic, punctuation, leukoplakia and atypical vascular areas. Patients with pathological colposcopic findings were monitored and treated in our center. Cervical biopsy samples were sent to the pathology unit in formaldehyde for evaluation, and biopsies were evaluated by 4 cytopathologists experienced in gynecological oncology.

One hundred sixty-nine ASC-H patients underwent follow-up tissue sampling, including colposcopic biopsy, Loop Electrosurgical Excision Procedure (LEEP), conization, and hysterectomy. LEEP tissue sampling presented satisfactory samples in HSIL cases, and the squamo-columnar junction was not deeper than the first centimeter level of the cervical canal. Conization was performed in cases with deeper problems in LEEP. Radical pelvic surgery was performed in patients with adenocarcinoma and squamous cell carcinoma. The diagnosis obtained from histological specimens were taken as the gold standard. If the cases were analyzed using histology and had more serious findings, later procedures were accepted as definitive diagnosis. Cases with normal histological samples were taken as negative results.

Statistical analysis

Statistical analysis of the data was performed by SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA). Descriptive statistics are presented as mean ± standard deviation and median (min-max) for continuous variables and as numbers and percentages for categorical data. The distribution of normality of data for statistical test selection was evaluated by Kolmogorov-Smirnov and Shapiro-Wilk tests. The t-test was used to compare the age of the patients according to the HPV groups. Correlation studies between categorical variables and ratio comparisons were performed using Chi-squared test or Fisher exact test. The relationship between HPV type according to pathology result and age was examined by general linear model. Statistical significance level was accepted as $p < 0.05$.

3. Results

169 patients were included in the study. Demographic data and clinical characteristics of the patients according to HSIL pathologic results are shown in Table 1. There was no significant difference between age groups ($p = 0.425$). There was no significant relationship between biopsy results and educational status, financial status and smoking ($p = 0.320$, $p = 0.342$, $p = 0.214$, respectively). The distribution of pathologic findings and patients age according to hrHPV and lrHPV results is shown in Table 2. There was a statistically significant difference between the groups in terms of age (34.77±5.47 vs 31.78±8.22 $p = 0.004$). Cervical biopsy was performed in all the patients who participated in the study and 62 of these cases were diagnosed with HSIL and cervical carcinoma, while the remaining 107 had LSIL and other benign lesions (Table 2).

Table 1. Clinical characteristics of study population (n=169) and demographic data and evaluation of biopsy.

		<HSIL	≥HSIL	P-value
Age Mean ± SD (min-max)		33.32 ± 3.80 (30-44)	34.24 ± 4.30 (30-46)	0.425
Age of first intercourse Mean ± SD (min-max)		20.14 ± 1.48 (16-27)	21.02 ± 1.76 (16-29)	0.352
BMI Mean ± SD (min-max)		27.22 ± 2.43 (19.9-32.3)	26.18 ± 2.78 (19.4-31.7)	0.480
Gravida Mean ± SD (min-max)		2.44± 1.10 (0-5)	2.38 ± 1.19 (0-5)	0.256
Parity Mean ± SD (min-max)		2.18 ± 0.88 (0-5)	2.15 ± 0.95 (0-5)	0.282
Abortion Mean ± SD (min-max)		2.33 ± 0.85 (0-4)	2.12 ± 0.95 (0-5)	0.278
Education n, (%)	Less than high school	52(30.7)	25(14.8)	0.320
	High school	49(28.9)	33(19.6)	
	University	6(3.6)	4(2.4)	
Wage, dollars n, (%)	<500	51(21.3)	35(19.5)	0.342
	500-1000	45(25.5)	30(26.7)	
	1000<	5(3)	3(4.1)	
Smoking n, (%)	Smoking	24(6.5)	14(8.3)	0.214
	Non-smoking	73(43.8)	48(41.4)	

Data are presented as mean ± standard deviation, SD: standard deviation, min: minimum, max: maximum. A P value of <0.05 was considered as statistically significant.
Abbreviation: BMI, body mass index; ASC-H, atypical squamous cells when high-grade intraepithelial lesions (ASC-H) cannot be ruled out; HSIL, high-grade squamous intra-epithelial lesions.

Table 2. Age and biopsy results according to HPV types

		lrHPV (N=51)	hrHPV (N=118)	P-value
Age Mean ± SD, (min-max)		34.77±5.47 (29-40)	31.78±8.22 (23-40)	0.004
Cervical biopsy results	<HSIL n, (%)	42(24.9%)	65 (38.4%)	0.031
	Benign	21 (12.45%)	27 (16%)	
	LSIL	21 (12.45%)	38 (22.4%)	
	≥HSIL n, (%)	9(5.3%)	53(31.4%)	
	HSIL	9 (5.3%)	47 (27.9%)	
	Squamous CA	/	5 (3%)	
	Adeno CA	/	1 (0.5%)	

Data are presented as mean ± standard deviation, SD: standard deviation, min: minimum, max: maximum. A P value of <0.05 was considered as statistically significant.
Abbreviation: HPV, Human Papilloma Virus; : <HSIL: normal histopathological findings or histopathological low-grade squamous intraepithelial lesion (LSIL); ≥HSIL, histopathological HSIL, squamous cell carcinoma, adenocarcinoma; hrHPV, High-risk HPV types (oncogenic or cancer-associated); lrHPV, Low-risk HPV types (nononcogenic or noncancer-associated); Squamous CA, squamous cell carcinoma; Adeno CA, Adenocarcinoma. hrHPV types are HPV DNA type 16, 18, 31, 33,35, 45, 51, 58, 59 and 68, lrHPV types are HPV DNA type 6, 11, 40, 54 and 70.

General linear regression analysis revealed that HSIL biopsy results were significantly correlated with HPV in patients with high risk (p=0.031) and that age and combined age and hrHPV presence were not affected the biopsy result (p=0.746 and p=0.349 respectively) (Table 3). In our study, no significant correlation was found between age and biopsy results in linear regression analysis (Table 3).

Table 3. General linear regression analyses of HSIL cervical biopsy results and age and HPV types.

	F-value	P-value
Age	0.168	0.746
hrHPV	5.750	0.031*
Age +hrHPV	1.126	0.349

In patients with ASC-H, only hrHPV association with age or age does not affect the results of cervical biopsy.

4. Discussion

ASC is a spectrum of both benign and precancerous lesions and have relatively rare cytological interpretation with incidence rates of 0.27-0.6% among all pap tests with this cytological diagnosis (Solomon et al., 2002). It includes squamous metaplasia with degenerative properties, atrophic changes, reserve cell hyperplasia, reactive changes and hormonal effects as benign characteristics (Solomon et al., 2002; Massad et al., 2013). ASC-H represents 5-10% of ASC diagnoses, but the presence of pre-invasive lesions is more likely (Massad et al., 2013). The criteria for the diagnosis of ASC-H are variable (Fig.1 and 2). This diagnosis is defined as the presence of cell abnormalities that resemble high-grade lesions, but there are no definite criteria for such lesions (Gultekin et al., 2018).

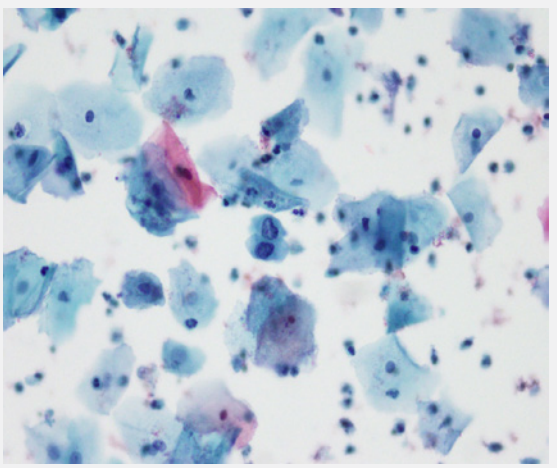

Fig. 1. Small, polygonal-shaped cells were observed on the floor consisting of polymorphonuclear leukocytes and mature squamous cells. The cytoplasms were dense and the nucleus/cytoplasm rates increased in favor of the nucleus.

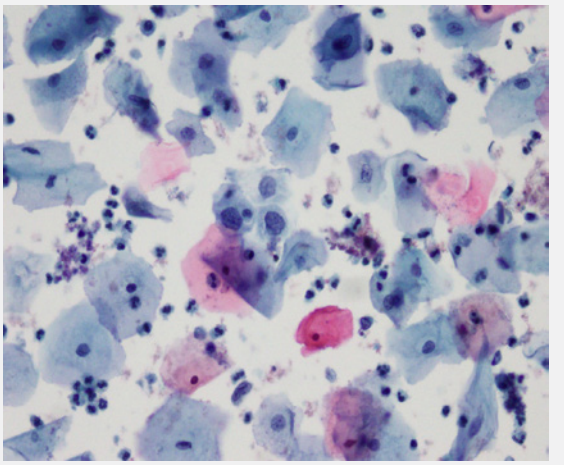

Fig. 2. The nuclei of the observed atypical squamous cells were large, the nuclear membranes were irregular, and the chromatin nets were rough.

The cytoplasm of cells in ASC-H are characteristically wider than in HSIL (Nieh et al., 2005). Because of the above-mentioned malignant and benign characteristics, the follow-up histology results of ASC-H cases are also highly variable and show significant differences in use between laboratories and in different clinical settings (Galliano et al., 2011). While some laboratories may see ASC-H as benign reactive processes, which can increase the ASC-H reporting rate, other laboratories may interpret some HSIL cases as ASC-H, resulting in a lower reporting rate (Koss, 1989).

62 (36.7%) of 169 patients were diagnosed as HSIL+. Cervical carcinoma was detected in 6 patients. These findings confirmed the opinion of referring all patients with ASC-H cytology to colposcopy and cervical biopsy. Histological follow-up studies of ASC-H cytology have shown that 70% of women show CIN 2 or above CIN 2 biopsy results and some studies have shown this to be a relatively high-risk category (Galliano et al., 2011; Gilani et al., 2014). In the study of Louro et al. 171 (79%) of 217 patients with ASC-H were found to have SIL or advanced lesions with biopsy results (Louro et al., 2003). In this study group, ASC-H ratio was reported as 0.84%. Saad et al. reported that in the comparison of premenopausal and postmenopausal PST results of biopsy results in patients with ASC-H, 22% of premenopausal patients and only 6% of postmenopausal patients were associated with HSIL (Saad et al., 2006). Young patients with ASC-H have been associated with a higher rate of HSIL than older women. Similarly, Selvaggi et al. Reported a high pre-prevalence of up to 68% in ASC-H patients in the young population aged 19-34 (Selvaggi et al., 2003).

In our study, we did not find a significant relationship between age and histopathology results. HrHPV positivity alone had an association with the degree of cervical biopsy results of patients with

ASC-H. In patients with ASC-H, hrHPV association only with age or age alone does not affect the results of cervical biopsy. Contrary to this finding, HrHPV positivity with younger age or age alone has no effect on the histopathology results of patients with ASC-H histology. On the contrary, Gilani et al. and Patton et al. found that advanced age was a determining risk factor for CIN in ASC-H patients (Patton et al., 2008; Gilani et al., 2014). The ALTS (ASCUS / LSIL Triage Study) study group reported that age was an important parameter in these patients and that the hrHPV rate was 85% in patients 35 years old and younger with ASC-H, while it decreased to 40% over the age of 35. The ALTS group identified a 40.5% risk of CIN 2+ lesion diagnosis in a patient with ASC-H and pointed out the need for studies to increase the efficiency of HPV DNA testing in the group over 35 years of age (Solomon et al., 2002; Sherman et al., 2001). Sung et al. suggested that the hr-HPV DNA test and p16INK4a test may be preferred for their higher specificity than HC2 and that these tests should be re-checked after 6-12 months if found negative (Sung et al., 2010). The rate of hr-HPV positivity in women with ASC-H cytology varies across the population (51-90%), and hr-HPV (+) was detected in 118 (66.2%) of 169 patients undergoing HPV testing in our study. It has been shown that the prevalence of ≥ CIN 2 is in a wide range (13-66%, mean value 34%) in women with ASC-H cytology (Patton et al., 2008; Gilani et al., 2014). In our study, this rate was found as 36.7%.

Follow-up results of patients diagnosed with ASC-H in pap smear test vary between studies. Mokhtar et al. reported that 59.4% of 123 cases diagnosed as cytologically ASC-H were reported as HSIL in subsequent biopsies (Mokhtar et al., 2008). Cytryn et al. showed that the prevalence of CIN 2/3 was 19.3% in 57 patients with ASC-H cytology (Cytryn et al., 2009). Kietpeerakool et al. reported the underlying prevalence of CIN 2 or higher lesions as 69.4% in 69 ASC-H patients. In this study, HSIL was relatively low compared to previous studies, which ranged from 24% to 94% (Kietpeerakool et al., 2008). Sun et al. reported that 52.3% of patients under 40 years of age with ASC-H in Pap smear had preinvasive lesions such as HSIL and higher (Sun et al., 2011). We think that the underlying reason for the high incidence of HSIL in our study may be related to the fact that the subjects were under 40 years of age. However, considering that we could not find any difference between the results of biopsy in patients under 30 years and 30-40 years of age, we conclude that smear interpretations with ASCH should be used more carefully in patients under the age of 40.

HPV test results are another helpful method for assessing the risk level of the ASC-H category. Gilani et al. found a high predictive value (87.2%) of the HPV test for the diagnosis of CIN in patients with ASC-H and suggested that these patients should be followed closely and carefully (Gilani et al., 2014). The American Society for Colposcopy and Cervical Pathology (ASCCP) recommends that women with ASC-H pap smears be evaluated by colposcopy regardless of performing HPV test (Wright et al., 2007). According to the ASCCP assessment, HPV (-) ASC-H patients have a higher risk of cervical cancer than expected, and HPV testing in ASC-H patients is already high (+) in studies, and HPV testing is not mandatory. Colposcopic examination instead of follow-up is appropriate for the benefit of the patient (Wright et al., 2007). However, there are also some reports advocating that these patients should be evaluated by HPV test even if they were examined by colposcopy (Louro et al., 2003; Milutin et al., 2008; Gultekin et al., 2018)

Although our approach was to apply colposcopy to all ASCH patients in accordance with ASCCP recommendations, colposcopic evaluation was recommended in patients with persistent cytological abnormalities in repeated tests or if the HPV test was positive in a study that opposed this opinion (Wright et al., 2007).

In the context of possible outcomes, this study has a few more values. Considering the inclusion of many registered young patients and the similar appearance of ASCH with secondary changes such as metaplasia, inflammation and atrophy, the exclusion of this group of patients was an important addition to the literature on this subject. First, a homogeneous condition was studied, although it had a retrospective design. Patients were selected between 23-40 years of age, and perimenopausal and/or postmenopausal patients were excluded from the study; therefore, our study was composed of younger patients. We analyzed all samples with the same instrument for the entire study period and for the entire study group. In addition, we excluded several obstetric and medical conditions that had the potential to influence the parameters examined, which also increase the quality of our study. Factors such as hormone replacement therapy are less likely to affect the outcome of the study. These secondary changes are more common in older women, which may explain why ASC-H has a higher incidence of HSIL in younger patients. Although ASC-H is in clinical use due to its association with underlying HSIL, it is still difficult to predict ASC-H results. This study showed that ASC-H was closely related to HSIL or higher lesions, especially in young (under 40) women with positive smear testing for HPV DNA.

Our study had some limitations. First, the study may have been affected by lifestyle and the number of partners. Second, this study was conducted in a single institution. We believe that the results of this study may help the early and effective treatment of ASC-H. The

performance of the markers used in this study in multi-center studies will strengthen our results.

Since HPV test was studied together with cytology as a co-test in some cases, the limited number of patients was among the missing elements of our study. In conclusion, patients with ASC-H cytology carrying hr-HPV had a risk of 2.647-fold in terms of ≥ CIN 2 lesions compared to patients without hr-HPV. Considering our study and the current literature, colposcopic evaluation is an indispensable step since ASC-H patients have a high risk of ≥ CIN 2 lesions. Performing HPV test in ASC-H patients may lead us to minimize errors and discrepancies in cytology and colposcopy. With national cervical cancer screening in our country, it is thought that conducting large series of studies including the value of HPV test on ASC-H patients in the following years will contribute to science not only in our country but also in the world. In conclusion, patient age, positive HPV DNA test and recurrent abnormal cytology may help predict the underlying pathology of HSIL or higher lesions in women with ASC-H.

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REFERENCES

Apgar, B.S., Zoschnick, L., Wright, T.C., 2003. The 2001 Bethesda system terminology. Am. Fam. Physician. 68, 1992-1998.

Chang, O.S., Young, L.O., Sang, Y.S., 2011. Cervical cytology of atypical squamous cells cannot exclude high-grade squamous intra-epithelial lesion: Significance of age, human papillomavirus DNA detection and previous abnormal cytology on follow-up outcomes Eur. J. Obs. Gyn. Rep. Biol. 159, 155–159.

Cytryn, A., Russomano, F.B., Camargo, M.J., 2009. Prevalence of cervical intraepithelial neoplasia grades II/III and cervical cancer in patients with cytological diagnosis of atypical squamous cells when high-grade intraepithelial lesions (ASC-H) cannot be ruled out. Sao Paulo Med. J. 127, 283–287.

De Sanjose, S., Serrano, B., Castellsague, X., Brotons, M., Munoz, J., Bruni, L., Bosch, F.X., 2012. Human papillomavirus and related cancers in the global alliance for vaccines and immunisation (GAVI) countries, a who and ICO HPV information centre report. Vaccine.11, D1–83.

Forman, D., de Martel, C., Lacey, C.J., Soerjomataram, I., Lortet-Tieulent, J., Bruni, L., Vignat, J., 2012. Global burden of human papillomavirus and related diseases. Vaccine. 30, 12–23.

Galliano, G.E., Moatamed, N.A., Lee, S., Salami, N., Apple, S.K., 2011. Reflex high risk HPV testing in atypical squamous cells, cannot exclude high grade intraepithelial lesion: a large institution's experience with the significance of this often ordered test. Acta Cytol. 55, 167–172.

Gilani, S.M., Tashjian, R., Fathallah, L., 2014. Cervical cytology with a diagnosis of atypical cells, cannot exclude highgrade squamous intraepithelial lesion (ASC-H): A followup study with corresponding histology and significance of predicting dysplasia by human papillomavirus (HPV) DNA testing. Arch. Gynecol. Obstet. 289, 645-648.

Gultekin, M., Zayifoglu, K.M., Dundar, S., Boztas, G., Semra, T.H., Hacikamiloglu, E., Murtuza, K., Keskinkilic, B., Sencan, I., 2018. Initial results of population based cervical cancer screening program using HPV testing in one million Turkish women. Int. J. Cancer. 142, 1952-1958.

Kietpeerakool, C., Srisomboon, J., Tantipalakorn, C., Suprasert, P., Khunamornpong, S., Nimmanhaeminda, K., 2008. Underlying pathology of women with ''atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion'' smears, in a region with a high incidence of cervical cancer. J. Obstet. Gynaecol. Res. 34, 204–209.

Koss, L.G., 1989. The Papanicolaou test for cervical cancer detection. A triumph and a tragedy. JAMA. 261, 737-43.

Louro, A.P., Roberson, J., Eltoum, I., Chhieng, D.C., 2003. Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion. A follow-up study of conventional and liquid-based preparations in a high-risk population. Am. J. Clin. Pathol. 120, 392-397.

Massad, L.S., Einstein, M.H., Huh, W.K., Katki, H.A., Kinney, W.K., Schiffman, M., Solomon, D., Wentzensen, N., Lawson, H.W., 2013. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J. Low Genit. Tract. Dis. 17, 1-27.

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

Mokhtar, G.A., Delatour, N.L., Assiri, A.H., Gilliatt, M.A., Senterman, M., Islam, S., 2008. Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion: Cytohistologic correlation study with diagnostic pitfalls. Acta Cytol. 52, 169-177.

Nieh, S., Chen, S.F., Chu, T.Y., Lai, H.C., Lin, Y.S., Fu, E., Gau, C.H., 2005. Is p16 (INK4A) expression more useful than human papillomavirus test to determine the outcome of atypical squamous cells of undetermined significance-categorized Pap smear? A comparative analysis using abnormal cervical smears with follow-up biopsies. Gynecol. Oncol. 97, 35–40.

Papanicolaou, G.N., Traut, H.F., 1997. The diagnostic value of vaginal smears in carcinoma of the uterus. 1941. Arch. Pathol. Lab. Med. 121, 211-224.

Patton, A.L., Duncan, L., Bloom, L., Phaneuf, G., Zafar, N., 2008. Atypical squamous cells, cannot exclude a high-grade intraepithelial lesion and its clinical significance in postmenopausal, pregnant, postpartum, and contraceptive-use patients. Cancer. 114, 481–488.

Saad, R.S., Dabbs, D.J., Kordunsky, L., Kanbour-Shakir, A., Silverman, J.F., Liu, Y., Kanbour, A., 2006. Clinical significance of cytologic diagnosis of atypical squamous cells, cannot exclude a high grade squamous intraepithelial lesion in perimenopausal and postmenopausal women. Am. J. Clin. Pathol. 126, 381–388.

Selvaggi, S.M., 2003. Reporting of atypical squamous cells, cannot exclude a high-grade squamous intraepithelial lesion (ASC-H) on cervical samples: Is it significant? Diagn. Cytopathol. 29, 38-41.

Sherman, M.E., Solomon, D., Schiffman, M., 2001. A comparison of equivocal LSIL and equivocal HSIL cervical cytology in the ASCUS LSIL Triage Study. Am. J. Clin. Pathol. 116, 385–394.

Solomon, D., Davey, D., Kurman, R., Moriarty, A., O'Connor, D., Prey, M., Raab, S., Sherman, M., Wilbur, D., 2002. The 2001 Bethesda System: Terminology for reporting results of cervical cytology. JAMA. 287, 2114-2119.

Sung, C.O., Kim, S.R., Oh, Y.L., Song, S.Y., 2010. The use of p16INK4a immunocytochemistry in atypical squamous cells which cannot exclude HSIL [compared with Batypical squamous cells of undetermined significance] in liquid-based cervical smears. Diagn. Cytopathol. 38, 168-171.

Waxman, A.G., 2005. Guidelines for cervical cancer screening, history and scientific rationale. Clin. Obstet. Gynecol. 48, 77-97.

Wright, T.C., Massad, S., Dunton, C.J., Spitzer, M., Wilkinson, E.J., Solomon, D., 2007. For the 2006 American Society for Colposcopy and Cervical Pathology-sponsored Consensus Conference. Consensus guidelines for the management of women with abnormal cervical screening tests. J. Low Genit. Tract. Dis. 11, 201-22.

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Case Report

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Endovascular treatment of basilar artery aneurysm via the persistent trigeminal artery: A case report

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ABSTRACT

An 85-year-old woman presented to emergency department of our hospital with a sudden onset headache and temporary loss of consciousness. Brain CT scan revealed subarachnoid hemorrhage (SAH) located in the left ambient and quadrigeminal cisterns. Brain CT angiography revealed a narrowed-necked aneurysm measuring 3.5.x4.5x5 mm detected at the junction of the basilar artery (BA) and the left superior cerebellar artery (SCA). Both of the vertebral arteries were hypoplastic, and also proximal half of the BA was absent. Distal half of it was associated with a persistent trigeminal artery (PTA) located on the right side. The aneurysm of the basilar artery which could not be reached via the vertebral artery was embolized with detachable coils using primitive trigeminal artery. The cases with PTA are often discovered incidentally on imaging. Symptomatic cases often present with the signs of vertebrobasilar ischemia, cranial nerve palsy or rupture of the concomitant aneurysm. A BA aneurysm associated with PTA is very rare. Our case is also the second case treated endovascularly via the PTA.

1. Introduction

In an embryo, there are transitory vessels those connect the developing carotid arteries and the precursor of the basilar artery (BA). These vessels regress during embryogenesis, most commonly. However, a very small portion of them may persist, so-called persistent carotid-vertebrobasilar anastomoses (PCVBA) (Aguilar et al., 2011; Takigawa et al., 2014). They may be associated with several cerebral vascular pathologies, such as vertebral artery hypoplasia, cerebral aneurysm and arteriovenous malformation (Ikushima et al., 2002; Takigawa et al., 2014). In such cases, aneurysms are usually localized to the Willis polygon or the persistent trigeminal artery (PTA), the most common PCVBA. In this regard, accompanying posterior circulation aneurysms are very rare. In this case report, our aim is to present a patient with a ruptured BA aneurysm accompanied by a PTA, and to describe endovascular treatment of her.

2. Case

An 85-year-old woman presented to emergency department of our hospital with a sudden onset headache and temporary loss of consciousness. Non-contrast-

enhanced CT of the brain revealed subarachnoid hemorrhage (SAH), which was more prominent in the left ambient and quadrigeminal cisterns. On CT angiography of the brain, a narrowed-necked aneurysm measuring 3.5.x4.5x5 mm was detected at the junction of the BA and the left superior cerebellar artery (SCA). Both of the vertebral arteries were hypoplastic, and also proximal half of the BA was absent. Distal half of it was associated with a PTA located on the right side. The patient was consulted with us by the referring neurosurgeon, and endovascular approach was found to be favourable for the treatment.

The patient was admitted to the angiography suite 2 days after the bleeding. Under general anesthesia, a 6-Fr long introducer sheath was inserted into her right common carotid artery by the femoral access route, and then a 5-Fr guiding catheter (Navien, Covidien, California, USA) was inserted prior to the orifice of the PTA via the right internal carotid artery. Subsequently, a 2.1 Fr microcatheter (Echelon 10, Covidien, California, USA) was introduced into the aneurysm sac via the PTA. The aneurysm sac was completely embolized by using multiple detachable coils (MicroVention, Aliso Viejo, CA) (Fig. 1). The procedure ended without any complications.

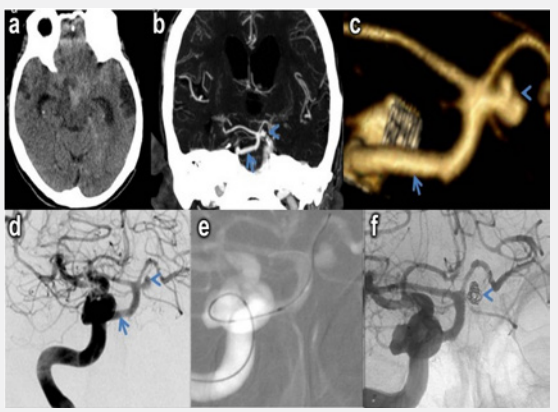

Fig. 1. Brain CT scan shows subarachnoid hemorrhage located in the left ambient and quadrigeminal cisterns (a). Brain CT angiography (b,c) and digital substraction angiography (d) show the persistent primitive trigeminal artery (arrow) originating from the right internal carotid artery, displastic basilar artery and 3,5x4,5x5 mm saccular aneurysm (arrowhead) at the junction of the basilar artery-the left superior cerebellar artery. Final angiograms shows catheterization of the aneurysm through PTA and complete occlusion of the aneurysm after coils placement (e,f).

3. Discussion

In an adult, except for the posterior communicating artery (PComA), an anastomosis between the anterior and the posterior circulation reflects the persistence of the embryonic arteries which could not regress due to anomalous embryological development of the posterior circulation. Such an anastomosis, so-called PCVBA, may be formed by four different arteries, and are as follows: persistent trigeminal artery, persistent otic (acoustic) artery, persistent hypoglossal artery and persistent proatlantal artery, in craniocaudal order. The arteries are named, with the exception of the last one, using the cranial nerves with which they run (Padget, 1948). Among these, PTA is the most common one with an incidence ranging from 0.1 to 0.6 percent (Aguilar et al., 2011; Takigawa et al., 2014). In the cases with PTA, ipsilateral PComA, ipsilateral vertebral artery or the BA are usually aplastic or hypoplastic (Ali et al., 2008; Aguilar et al., 2011; Azab et al., 2012).

Persistent trigeminal artery was described by Padget, however, the classification system developed by Saltzman is being used today (Padget, 1948; Saltzman, 1959). Saltzman defined three types of PTA according to the localization of the anastomosis and the presence of the PComA. In type 1 PTA, it joins the BA between the origins of the anterior inferior cerebellar artery (AICA) and the SCA. In this case, the section of the BA proximal to the anastomosis is hypoplastic, and the SCA and the posterior cerebral artery (PCA) is fed by PTA. In type 2 PTA, it joins the BA at the level of the SCA orifice, and the BA is absent below this point. The PCA is fed by the ipsilateral PComA. In type 3 PTA, we come across with a combination of the type 1 and 2, so-called PTA variant. In this type, PTA does not directly join the BA but establishes a connection with the SCA, the AICA or the posterior inferior cerebellar artery (Ali et al., 2008; Azab et al., 2012; Hwang and Kim, 2016). In type 3 PTA, the PComA is patent (Siqueira et al., 1993). In our case, the PTA joined middle third of the BA, and the section of the BA proximal to the anastomosis was agenetic. On both sides, any PComA was not present. The posterior cerebral circulation was supplied by the PTA via the right internal carotid artery. Our case was found to be compatible with the Saltzman type 1.

The cases with PTA are often discovered incidentally on imaging done for non-related causes, as the patients are frequently asymptomatic (Cloft et al., 1999). Symptomatic cases often present with the signs of vertebrobasilar ischemia, cranial nerve palsy or rupture of the concomitant aneurysm with the latter being the most common type of presentation (Ali et al., 2008; Pleş et al., 2015). The incidence rate of aneurysms associated with PTA is reported to be up to 14%. It is thought that altered flow dynamics due to aplasia or hypoplasia of the vertebrobasilar arteries trigger aneurysm formation. In such cases, aneurysms are most commonly localized to the arteries of the Willis polygon. Only 1% of these aneurysms are localized to the trigeminal artery itself (Tubbs et al., 2011). A BA

aneurysm associated with PTA is very rare, and, as far as we know, this is the second case where there is such a co-existence (Hanabusa et al., 2000; Kim et al., 2010; Aguilar et al., 2011).

Because of the difficulty accessing the aneurysm and the proximity to the brain stem, endovascular approach is the preferred mode of therapy in posterior system aneurysms. In evaluating the mode of endovascular treatment, the access route is decisive. In our case, the only access route to catheterize the aneurysm sac was the PTA itself because the BA section proximal to the anastomosis was aplastic. In the management of the aneurysm, primary coil embolization was preferred, since the aneurysm was narrow-necked. Ikushima et al. (2002) presented a case treated with coil embolization in whom there was an aneurysm at the same location like our case, in 2002. Our case is also the second case treated endovascularly via the PTA.

In conclusion, aneurysms associated with PTA can be localized to the BA itself, and these aneurysms can be successfully treated with endovascular method via the PTA. To know the possible variations of the PTA is crucial in determining the endovascular treatment strategy.

REFERENCES

Aguilar, G.B., Conti, M.L., Veiga, J.C., Jory, M., Souza, R.B., 2011. Basilar artery aneurysm at a persistent trigeminal artery junction. A case report and literature review. Interv. Neuroradiol. 17, 343-346.

Takigawa, T., Suzuki, K., Sugiura, Y., Suzuki, R., Takano, I., Shimizu, N., Tanaka, Y., Hyodo, A., 2014. Double-balloon remodeling for coil embolization of a primitive trigeminal artery variant aneurysm a case report. Interv. Neuroradio. 20, 295-300.

Ikushima, I., Arikawa, S., Korogi, Y., Uehara, H., Komohara, Y., Takahashi, M., 2002. Basilar artery aneurysm treated with coil embolization via persistent primitive trigeminal artery. Cardiovasc. Interv. Radiol. 25, 70-71.

Padget, D.H., 1948. The development of the cranial arteries in the human embryo. Contrib. Embryol. 32, 205-262.

Hwang, Y.U., Kim, J.W., 2016. Variant PTA terminating in cerebellar artery, associated with multiple aneurysms. Case Rep. Radiol. 2016, 4594326.

Azab, W., Delashaw, J., Mohammed, M., 2012. Persistent primitive trigeminal artery: A review. Turk. Neurosurg. 22, 399-406.

Ali, S., Radaideh, M.M., Shaibani, A., Russell, E.J., Walker, M.T., 2008. Persistent trigeminal artery terminating in the posterior inferior cerebellar artery: Case report. Neurosurgery. 62, 746-748.

Saltzman, G.F., 1959. Patent primitive trigeminal arteries studied by cerebral angiography. Acta Radiol. 51, 329-336.

Siqueira, M., Piske, R., Ono, M., Marino, Júnior, R., 1993. Cerebellar arteries originating from the internal carotid artery. AJNR Am. J. Neuroradiol. 14,1229-1235.

Cloft, H.J., Razack, N., Kallmes, D.F., 1999. Prevalence of cerebral aneurysms in patients with persistent primitive trigeminal artery. J. Neurosurg. 90, 865-867.

Pleş, H., Loukas, M., Andall, R.G., Andall, N.R., Iacob, N., Miclăuş, G.D., Matusz, P., Tubbs, R.S., 2015. Fusiform aneurysm of a persistent primitive trigeminal artery associated with cerebrovascular anatomic variations: A report of two cases. Rom. J. Morphol. Embryol. 56, 1159-63.

Tubbs, R.S., Verma, K., Riech, S., Mortazavi, M.M., Shoja, M.M., Loukas, M., Curé, J.K., Zurada, A., Cohen-Gadol, A.A., 2011. Persistent fetal intracranial arteries: A comprehensive review of anatomical and clinical significance. J. Neurosurg. 114, 1127–1134.

Kim, B.M., Kim, D.I., Kwon, T.H., 2010. Persistent trigeminal artery with a cerebellar branch and trigeminal-cavernous fistula from ruptured aneurysm: Transarterial coil embolization. Neurointervention. 5, 32–35.

Hanabusa, K., Murao, K., Morikawa, A., Taki, W., Waga, S., 2000. Endovascular treatment for a ruptured persistent trigeminal artery variant aneurysm on the distal portion-case report. Neurol. Med. Chir. 40, 637-640.

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Case Report

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A two days old newborn with partial biotinidase deficiency presenting with treatment resistant convulsions

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ABSTRACT

Biotinidase deficiency (BD) is an autosomal recessive metabolic disorder characterized primarily by cutaneous and neurologic abnormalities (OMIM 253260). Symptoms usually appear by three months of age (minimum 12th day) with seizures as the most frequent initial symptom. We decided to present a patient with partial biotinidase deficiency since she presented with neurological findings as early as the second day of life in order to discuss the additional factors leading to such early signs. The baby was born via normal spontaneous delivery as the second child from nonconsanguineous healthy parents; a 33-year-old mother and 35-year-old father with a birth wieght was 3440 g. Her first clinical symptoms were cyanosis and tonic convulsions after feeding on the second day. Both her parents and her 17-month-old brother were healthy. On physical examination 1/6 pansistolic murmur was heard, diaper dermatites and sacral dimple was observed as well. She was admitted to Neonatal Intensive Care Unit (NICU) for the investigation and treatment of neonatal convulsion. Despite the use of phenobarbital and levetiracetam, apnea and generalized convulsions occurred thrice in the NICU. Biochemical evaluation during these convulsions revealed hypoglycemia (49 mg/dl) and hyperammonemia (150 mcmol/L); albeit her carnitine and aminoacid profile were nonspecific. Her further neurological evaluation by electroencephalography, and cranial magnetic resonance imaging was normal. Seizures were controlled with biotin and folate therapy. Final laboratorial evaluation showed a biotinidase activity of 2.60U/L, (3.5-13.80) and the genetic tests c.1330 G>C (p.Asp444His heterozygous) were related with biotinidase deficiency and A1298 C, C677T compound heterozygous mutations related to Methylene tetra hyrofolate deficiency (MTHFR). Both biotinidase deficiency and MTHFR may cause convulsions. However, the presence of neurologic symptoms as early as the second day of life has not been reported for both before. The coexistence of these diseases, which may cause similar neurological findings, should be investigated as a cause of early clinical findings. Until a satisfactory answer to this question is found, biotin and folate may be considered as a treatment option for early neonatal convulsions and coexistence of the biotinidase deficiency and MTHFR mutations should be investigated.

1. Introduction

Biotinidase, which is vital for the recycling of biotin, cleaves biotin from biocytin. Biotin acts as a prosthetic group in each of four carboxylases involved in the amino acid catabolism, fatty acid synthesis and gluconeogenesis. Biotinidase deficiency (BD) is an autosomal recessive disorder that is responsive to biotin treatment (OMIM 253260; Wolf et al., 1985; Wolf et

al., 2001). According to enzyme activity level, two types of BD are described: Less than 10% biotinidase activity is profound deficiency and 10-30% of mean normal activity is partial defficiency. Children with partial BD are at an increased risk of developing the same symptoms of profound deficiency. However, the appearance of symptoms seems to be associated with metabolic stressors (eg, illness, fever, fasting), and children may not be symptomatic until then (Swango et al., 1998). The spectrum of clinical signs and symptoms is variable. BD should be considered at presentation of intractable seizures, acidosis, rash, unexplained hearing or visual loss, spastic paraparesis, failure to thrive or sudden death (Burton et al., 1987; Hoffman et al., 2005). Patients usually present with lactic acidosis, hyperammonemia and a characteristic organic aciduria, in which lactic acid, 3-OH-isovaleric acid, methylcrotonylglycine, methylcitrate are the key metabolites. In children with BD, cerebral edema, low attenuation of white matter signal, cerebral atrophy, and compensatory ventricular enlargement can be observed in magnetic resonance imaging (MRI). Magnetic resonance spectroscopy (MR-S) also helps to determine the functional metabolism of the brain. Visual and hearing disturbances are investigated by Visual Evoked Potential (VEP), Electro Retinography (ERG) and Brain Stem Evoked Response Audiometry (BERA) (OMIM 253260; Burton et al., 1987; Dunkel et al., 1989; Wolf et al., 2001; Heller et al., 2002; Hoffman et al., 2005; Kalkanoğlu et al., 2007). Delay in the diagnosis of BD may lead to seizures, hypotonia, developmental delay, visual and hearing abnormalities, alopecia and skin rash, and eventually death. Contrarily, with treatment, patients have an excellent prognosis and potential for a normal lifestyle (Sweetman et al., 1986; Bousounis et al., 1993).

Folic acid is important for the metabolism of monocarbon compounds required in the synthesis of sulfur amino acids, nucleic acids and intermediate metabolites. Folic acid is not synthesized in the body, it is taken inactively with food. The conversion of dihydrofolate (DHF) in the body to active tetrahydrofolate (THF) requires the aid of the enzyme Methylenetetrahydrofolate Reductase (MTHFR). The monocarbon compounds (methyl, methylene, methyl, formyl) separated at the same time, convert homocysteine to methionine in sulfur amino acid metabolism; thymidylate (dTMP), formylglycinamide ribotide (FGAR), formylaminoimidazole carboxamide ribotide (FAICAR). Methylene THF suppresses the progression of folate and pyrimidine synthesis if it does not convert to methyl THF (Rosenblatt et at., 2016). MTHFR cannot be converted to methionine by adding methyl to homocysteine in the absence of quantity or function; homocysteine rises in the blood, and methionine falls. In 1995, Frost et al., described the relationship between temperature and function decline (thermolability) to genetics for the MTHFR C677T mutation. MTHFR C677T variant is seen in 8-15% of the population (Frost et al., 1996). The homozygous mutation of this enzyme deteriorates the stability of MTHFR by the increase in temperature, decreases enzyme activity by 50%. TT genotype has been shown to cause both maternal (50%) and fetal (80%) neural tube defects (NTD). Another common pathology A1298C mutation decreases the enzyme activity (Weisberg et al., 1998; Bloom et al., 2006). Both mutations alone or together lead to an increase in NTD frequency through folate metabolism (Ozer et al., 2011). MTHFR polymorphism in those with B12, folate deficiency increases homocysteine (Motulsky et al., 1996), which normalizes with folate supplementation. This effect is probably due to the stabilization of the thermolabile enzyme (Guttormsen et al., 1996) by folate at high blood level. If the serum folate level is above 15.4 nM, it may neutralize the C677T mutation (Jacques et al, 1996; Holm et al., 2007).

2. Case

Our patient was the second live child of a 33-year-old mother born at 39th gestational week, born by normal spontaneous vaginal route. The pregnancy history was uneventful. In the second day, she had cyanosis and tonic seizure was observed. The patient was referred to our hospital from the hospital where she was born. Her birth weight was 3440 g. On admission, her body weight was 3400 grams (75-90p), her height was 49.5 cm (50-75p) and her head circumference was 33.7 cm (25-50p). Skin examination revealed prominent diaper dermatitis and the sacral midline was deep (Fig. 1). Cardiovascular system examination revealed a 1/6 systolic murmur. Other systems were unremarkable. In the family history, there was no

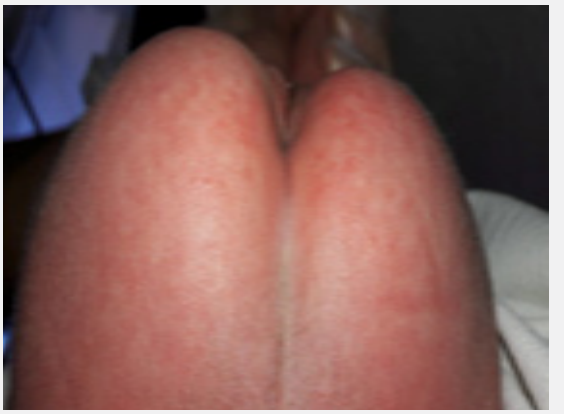

Fig. 1. Patient with prominent diaper dermatitis, deep sacral midline.

consanquinity between the 33-year-old mother and the 35-year-old father; her parents and 17-month-old sister were healthy. In the examinations of the patient, the patent foramen ovale associated with cardiac murmur was demonstrated by echocardiography. Direct laryngoscopic examination were normal.

On admission, biochemistry revealed a blood glucose level of 49 mg/dl; which did not recur. Simultaneously obtained insulin and C-peptide values were normal. Breastmilk was started as 8x10 cc, but she had three apnea attacks, causing desaturation. Oral feeding was stopped and intravenous dextrose support was increased to 8 mg/kg/minute. Transfontanel ultrasound and echocardiography were performed to explain the etiology of apnea; feature not found. A high ammonia level was detected during the evluation of hypoglycemia and she was consulted to the pediatric metabolism department. Oral feeding was discontinued for 2 days until metabolic tests were completed. Tandem mass with carnitine and aminoacid profile, urine organic acids by gas mass spectrophotometer and serum biotinidase activity by fluorimetric method, vitamin B12, folate, homocysteine, methylene tetra hydrofolate reductase mutation analysis was planned. During the clinical follow-up, the patient had seizures (cycling movements in four extremities) 3 times and phenobarbital was started. Brain magnetic resonance imaging (MRI) and electroencephalography (EEG) were ordered. Initial EEG and MRI were unremarkable. Epileptic activity was detected in the control EEG after 2 days; so levetiracetam was added to phenobarbital treatment by pediatric neurology department. Carnitine, biotin and folate were started by the pediatric metabolism department. Apnea attacks and seizures improved after biotine and folate supplementation. Breast milk was allowed since no specific pathology was oberved in metabolic basal tests. Nutritional tolerance was not a problem.

3. Results

Specific metabolic basal tests (serum ammonia, urine organic acids, plasma amino acids, urinary ketones, blood gases, biotinidase activity assey, carnitine, and acylcarnitine profiles) were demanded. Visual and hearing function were determinated by Visual Evoked Potential / Electroretinogram (VEP/ERG) and Brain Stem Evoked Response Audiometry (BERA); results were normal. Serum B12 level was 318 pg/ml (197-866), folate level was16.2 ng / ml (4.6-18.7); within the normal range; homocysteine was found at the upper limit: 12.47 mcmol / L (5-14). Final laboratorial evaluation showed that the patient's biotinidase activity was 2.60 U/L, (3.5-13.80) and her genetic evaluation revealed c.1330 G>C (p.Asp444His heterozygous) and MTHFR compound heterozygous mutations (Table 1).

Table 1. Pre treatment biochemical laboratory results of the patient

Test name and unit	Pretreatment results	References
Leucocyte/mm3	8690	4500-11000
Hemoglobine g/dl	16.1	11.5-14.5
Trombocyte /mm3	292,000	200-400 x103
Blood glocose mg/dl	49	60-100
Homocysteine mcmol / L	12.47	5-14
Urea mg/dl	6	<50
Creatinin	0.96	
Sodium mEq/L	134	134-146
Potassium Eq/L	4.89	3.5-5.2
Clor mEq/L	96.8	97-108
Phosphorus mg/dl	5.92	2.3-4.7
Calcium mg/dl	8.2	7.6-10.4
Magnesium mmol/L	0.83	0.7-1.05
Lactate mmol/L	2.41	5-14
25(OH) vitamin D3 mcg/L	9.23	30-80
Blood ammonia mcg/dl	150	18.7-86.9
Urine keton	Negative	
Blood pH	7.41	
Blood HCO3	23.1	
Serum B12 pg / ml	318	197-866
Folate ng / ml	16.2	4.6-18.7
Biotinidase activity U/L	2.60	3.5-13.80

4. Discussion

In Turkey both MTHFR and biotinidase deficiencies are more frequent when compared to other countries. Therefore, the probability of these two disorders, occuring in the same patient is higher in our country. The incidence of partial and profound deficiencies is 1 per 60,000 population in the world (Wolf et al., 1991), but 1/11.144 in Istanbul, Turkey (Baykal et al., 2005). Neonatal screening that was determined by Heard and colleagues is cost effective (Heard et al., 1986). Now screening for biotinidase deficiency is performed routinely in several countries around the world (Wolf et al., 1991), including Turkey.

Both biotinidase deficiency and MTHFR might lead to convulsions. However, neither of them had an early onset of neurological symptoms as early as the second postnatal day. The median age of clinical onset of BD is 3 months, but it can occur as late as 10 years of age. Initial symptoms have been reported as early as twelfth day of life (Baumgartner et al., 1985). This asemptomatic period allows sufficient time for early diagnosis and treatment and is important for neonatal screening programme.

Generalized convulsion, hypoglycemia, seizures, severe apnea requiring respiratory support and severe diaper dermatitis on the second postnatal day are reported for the first time in our patient. Intrauterine folate and B12 deficiency may cause perinatal convulsions. The mother does not have any nutritional habits or diseases that may lead to serious vitamin deficiency during pregnancy. On the contrary, she had used folic acid regularly during pregnancy and there was no problem in the intrauterine period.

Pisani et al., reported that the incidence of neonatal seizures was inversely related to gestational age and birth weight (Pisani et al., 2018).

We argue that two diseases, through different mechanisms, increased the risk of convulsions in our patient. Addition of the stress of labor caused the clinical findings to present very early. The rapid positive response to biotin and folate suplementation, especially the cessation of seizures and apnea attacks of the baby stands for this theory.

In conclusion; when BD and MTHFR deficiency, which may cause similar neurological symptoms, come together, the question of whether an early clinical finding occurs should be investigated. Until the satisfactory answer to this question is found, it is recommended to consider BD and MTHFR coexistence in the presence of early neonatal convulsions. We advice the addition of biotin and folate to the standard empirical neonatal convulsion treatment options.

REFERENCES

Baumgartner, E.R., Suormala, T., Wick, H., Bausch, J., Bonjour, J.P., 1985. Biotinidase deficiency: factors responsible for the increased biotin requirement. J. Inherit. Metab. Dis. 8, 59-64.

Baykal, T., Gokcay, G., Gokdemir, Y., Demir, F., Seckin, Y., Demirkol, M., Jensen, K., Wolf, B., 2005. Asymptomatic adults and older siblings with biotinidase deficiency ascertained by family studies of index cases. J. Inherit. Metab. Dis. 28, 903-912.

Blom, H.J., Shaw, G.M., den Heijer, M., Finnell, R.H., 2006. Neural tube defects and folate: case far from closed. Nat. Rev. 7, 724–731.

Bousounis, D.P., Camfield, P.R., Wolf, B., 1993. Reversal of brain atrophy with biotin treatment in biotinidase deficiency. Neuropediatrics. 24, 214-217.

Burton, B.K., Roach, E.S., Wolf, B., Weissbecker, K.A., 1987. Sudden death associated with biotinidase deficiency. Pediatrics. 79, 482-483.

Dunkel, G., Scriver, C., Clow, C., Melancon, S., Lemieux, B., Grenier, A., Laberge, C., 1989. Prospective ascertainment of complete and partial serum biotinidase deficiency in the newborn. J. Inherit. Metab. Dis. 12, 131–138.

Frosst, P., Zhang, Z.X., Pai, A., Rozen. R., 1996. The methylenetetrahydrofolate reductase (MTHR) gene maps to distal mouse chromosome 4. Mamm. Genome. 7, 864-869.

Guttormsen, A.B., Ueland, P.M., Nesthus, I., Nygard, O., Schneede, J., Vollset, S.E., Refsum, H. 1996. Determinants and vitamin responsiveness of intermediate hyperhomocysteinemia (equal to or greater than 40 micromole/liter): the Hordaland homocysteine study. J. Clin. Invest. 98, 2174-2183.

Heard, G.S., Wolf, B., Jefferson, L.G., Weissbecker, K.A., Nance, W.E., Napolitano, A., Mitchell, P.L., Lambert, F.W., Linyear, A.S., 1986. Neonatal screening for biotinidase deficiency: results of a 1-year pilot study. J. Pediatr. 108, 40-46.

Heller, A.J., Stanley, C., Shaia, W.T., Sismanis, A., Spencer, R.F., Wolf, B., 2002. Localization of biotinidase in the brain: implications for its role in hearing loss in biotinidase deficiency. Hear. Res. 173, 62-68.

Hoffman, T.L., Simon, E.M., Ficicioglu, C., 2005. Biotinidase deficiency: the importance of adequate follow-up for an inconclusive newborn screening result. Eur. J. Ped. 164, 298-301.

Holm, P.I., Hustad, S., Ueland, P.M., Vollset, S.E., Grotmol, T., Schneede, J., 2007. Modulation of the homocysteine-betaine relationship by methylenetetrahydrofolate reductase 677C-T geneotypes and B-vitamin status in a large-scale epidemiological study. J. Clin. Endocr. Metab. 92, 1535-1541.

Jacques, P.F., Bostom, A.G., Williams, R.R., Ellison, R.C., Eckfeldt, J.H., Rosenberg, I.H., Selhub, J., Rozen, R., 1996. Relation between folate status, a common mutation in methylenetetra hydrofolate reductase, and plasma homocysteine concentrations. Circulation. 93, 7-9.

Kalkanoğlu- Sivri, H.S, Aydan-Genç, G., Tokatlı, A., Dursun, A., Coşkun, T., Aydın, H.İ., Sennaroğlu, L., Belgin, E., Jensen, K., Wolf, .B 2007. Hearing loss in biotinidase deficiency: Genotype – phenotype correlation. J. Pediatr.150, 439-442.

Motulsky, A., 1996. Nutritional ecogenetics: homocysteine-related arteriosclerotic vascular disease, neural tube defects, and folic acid. Am. J. Hum. Genet. 58,17–20.

OMIM 253260 (http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=253260). Özer, I., Özçetin, M., Karaer, H., Kurt, S.G., Şahin, Ş., 2011. Retrospective approach to methylenetetrahydrofolate reductase mutations in children. Ped. Neuro. 45, 34-38.

Pisani, F., Facini, C., Bianchi, E., Giussani, G., Piccolo, B., Beghi, E. 2018. Incidence of neonatal seizures, perinatal risk factors for epilepsy and mortality after neonatal seizures in the province of Parma, Italy. Epilepsia. 59, 1764-1773.

Rosenblatt, D.S., Fowler, B., 2016. Disorders of cobalamin and folate transport and metabolism in: Jean-Marie Saudubray, Matthias R. Baumgartner, John Walter (eds). Inborn Metabolic Diseases, Springer Berlin, Heidelberg. 385-399.

Swango, K.L., Demirkol, M., Huner, G., Pronicka, E., Sykut-Cegielska, J., Schulze, A., Mayatepek, E., Wolf, B., 1998. Partial biotinidase deficiency is usually due to the D444H mutation in the biotinidase gene. Hum. Genet. 102, 571-575.

Sweetman, L., Nyhan, W.L., 1986. Inheritable biotin-treatable disorders and associated phenomena. Annu. Rev. Nutr. 6, 317-343.

Weisberg, I., Tran, P., Christensen, B., Sibani, S., Rozen, R., 1998. A second genetic polymorphism in methylenetetrahydrofolate reductase (MTHFR) associated with decreased enzyme activity. Mol. Gen. Metab. 64, 169–172.

Wolf, B., 2001. Disorders of biotin metabolism. In: Scriver, C., Beaudet, A., Sly, W., Valle, D. (eds). The metabolic and molecular Basies of inherited disease. McGraw-Hill, New York, 3935.

Wolf, B., Heard, G.S., Weissbecker, K.A., McVoy, J.R., Grier, R.E., Leshner, R.T., 1985.Biotinidase deficiency: initial clinical features and rapid diagnosis. Ann. Neurol. 18, 614-617.

Wolf, B., 1991. Worldwide survey of neonatal screening for biotinidase deficiency. JIMD. 14, 928-931.

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Case Report

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Addition of hyperthermic intraperitoneal chemotherapy (HIPEC) after complete cytoreductive surgery in a child with desmoplastic small round cell tumour

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Hyperthermic intraperitoneal chemotherapy
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ABSTRACT

Desmoplastic small round cell tumour (DSRCT) is a rare and aggressive sarcoma. No curative treatment has been reported yet; however, multi-agent chemotherapy, an aggressive surgical approach and radiotherapy have been used. Hyperthermic intraperitoneal chemotherapy (HIPEC) is an additional strategy used to remove microscopic disease after cytoreduction, especially in patients with peritoneal carcinomatosis and colorectal cancer; however, its application in paediatric patients has been reported rarely. In Turkey, some HIPEC studies have been performed in adult patients but not in paediatric patients. A 10-year-old girl presented to the hospital with a mass palpated in the left lumbar region. The mass was reported as a primitive neuroectodermal tumour after the biopsy. Left radical nephrectomy and lymph node dissection were performed after she failed to respond to five months of neoadjuvant chemotherapy. The pathological examination revealed a DSRCT. A multi-agent chemotherapy regimen was applied to the patient for one year. Myeloablative chemotherapy and autologous stem cell transplantation were performed in the patient, who subsequently entered remission. During the third month of follow-up, high-dose multi-agent chemotherapy protocols were initiated because of disease relapse. At 6 months after recurrence, HIPEC with irinotecan and oxaliplatin was performed after the excision of all tumour foci by intracavitary cytoreductive surgery. No complications were observed. The patient was prescribed a tyrosine kinase receptor inhibitor (sunitinib maleate). The patient died 8 months later. In conclusion, although the benefit of HIPEC is still unknown and requires evaluation in a prospective trial, HIPEC can be used as an alternative treatment in paediatric patients with peritoneal carcinomatosis.

1. Introduction

Desmoplastic small round cell tumour (DSRCT) is a rare and aggressive sarcoma commonly seen in children and adolescents (Gerald and Rosai, 1989). The prognosis of this disease is poor, with a median survival of approximately 17 months. Although the tumour is thought to be mesothelial in origin due to its frequent association with serosal surfaces, its origin

remains controversial. It has been hypothesised to have originated from a primitive cell with multipotent differentiation (Kim et al., 2009).

Because of anatomical and pathological polymorphisms, the differential diagnosis should be made based on immunohistochemical and cytogenetic studies according to the clinical and histological features of the disease (Gerald et al.,1995).

No curative treatment has been reported yet; multi-agent chemotherapy, an aggressive surgical approach and radiotherapy are among the current treatment options. As a multifaceted approach, hyperthermic intraperitoneal chemotherapy (HIPEC) is an additional strategy used to remove microscopic disease after cytoreduction, especially in patients with peritoneal carcinomatosis and colorectal cancer, but this treatment has been reported in very few patients (Reingruber et al., 2007). In Turkey, adult patients with DSRCT have been treated with HIPEC; however, this treatment has not been used in paediatric patients.

In this case report, we present our first HIPEC experience in a 10-year-old child with DSRCT in Turkey.

2. Case

A 10-year-old girl presented to the hospital with month-long fatigue, anorexia and back pain. A physical examination revealed a mass of approximately 10 × 10 cm palpated in the left lumbar region. Magnetic resonance imaging (MRI) showed a mass lesion of approximately 80x92×118mm encompassing nearly the entire left kidney and extending posteriorly, with solid components and cystic necrotic areas with heterogeneous contrast enhancement, irregular lobular contours and shifts in the left renal collecting system (Fig. 1). A soft tissue mass (conglomerate lymph nodes) of approximately 30×36×79mm was observed in the left para-aortic area on the medial segment of the mass, surrounding and compressing the left renal artery. Positron emission tomography/computed tomography (PET/CT) revealed multiple hypermetabolic foci in the lung and abdominal lymph nodes and multifocal hypermetabolic osseous lesions. The tumour was staged as T2bN1M1.

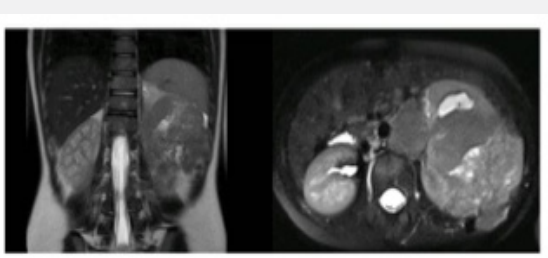

Fig. 1. MRI image of the mass.

An ultrasound-guided biopsy was performed on the mass, which was reported to be a primitive neuroectodermal tumour. Left radical nephrectomy and lymph node dissection were performed after six cycles of VIDE (vincristine 1.5 mg/m^2/day for 1 day, ifosfamide 3 g/m^2/day with mesna for 3 days and etoposide 150 mg/m^2/day for 3 days) administered according to the Euro-Ewing 99 protocol. Pathological examination using fluorescent in situ hybridisation of the nephrectomy material indicated a DSRCT with cytoplasmic reaction to the WT-1 dye and translocation of the ESWR gene. CEVAIE (carboplatin, epirubicin, vincristine, actinomycin-D, ifosfamide and etoposide), a multi-agent intensive chemotherapy regimen, was applied for approximately 1 year. At the end of the treatment, the fluorodeoxyglucose PET/CT findings were compatible with the radiological results and indicated a full remission with complete metabolic response. Because of the high risk of the disease metastasizing to sites other than the lung (tumour volume >100 ml), the decision to perform autologous stem cell transplantation was made by the council of the paediatric stem cell transplant centre. The procedure including busulfan (4 mg/m^2/d, 4 days) and melphalan (140 mg/m^2/d, 1 day) was successful. Three months after the transplantation, mass lesions were detected by abdominal MRI. A 19×16mm mass lesion with soft tissue intensity was detected in the liver in a subcapsular location at the anterior part of segment III. In addition, a 12×11mm mass lesion with soft tissue intensity and hyperintense in T2 series at segment IVB showed suspicious contrast enhancement after administering intravenous contrast agent. Furthermore, a 22×11mm mass at the medial, posterior and lateral parts of the spleen and at the hilus of the spleen between the pancreas and spleen and a 20×20mm soft tissue mass with hyperintensity and suspicious contrast enhancement was detected in the T2 series. Newly formed malignant hypermetabolic lesions were detected in the thorax, abdomen and skeletal system by PET/CT. Two cycles of salvage chemotherapy consisting of high-dose cyclophosphamide (2.1 g/m^2/d, 2 days) and topotecan (2 mg/m^2/d, 3 days) were applied to the patient. However, third-line chemotherapy, including irinotecan (175mg/m^2/d, 1 day) gemcitabine (1,000 mg/m^2/d, 1, 8, 15 days) and oxaliplatin (85mg/m^2/d, 1 day) (Carolin Hartmann et al., 2011), was performed due to the patient's poor response. However, widespread increased pathological metabolic activity (in multiple lung nodules and hilar lymph nodes, liver lesions, lesions adjacent to the spleen, abdominal lymph nodes, a mass adjacent to the rectum and foci of the skeletal system) was detected by PET/CT6 months after recurrence. This was interpreted as extensive progressive disease on abdominal MRI.

Cytoreductive surgery (CRS) and HIPEC were planned for the patient because of the overwhelming abdominal component. Informed consent was obtained from the patient's parents. Intraperitonealirinotecan (200 mg/m^2) and oxaliplatin (300 mg/m^2), which are activated by hyperthermia, were applied with the patient's prior chemotherapy protocol. Hypokalaemia caused by the tubular nephropathy, which developed from previously administered treatments, was corrected before the procedure. The high-dose saline infusion was applied before the procedure and continued for 48 hours after the procedure to reduce additional kidney toxicity potentially induced by the platinum-based drugs. First, omentectomy was performed by removing the omentum majus. The mass in the left upper quadrant was removed by mobilising the posterior part of the spleen. A portion of the distal pancreatic diaphragm was completely resected with the spleen. The liver metastases on both sides were excised by segmentectomy and transparenchymal dissection. The hilus of the liver and the lymph nodes on the hepatic artery were dissected. A peritoneal implant was detected, and a pelvic peritoneal mass between the bladder and rectum was excised. All parts of the abdomen were washed and haemostatic control was obtained. Because of diaphragm resection, a thoracic tube was placed and pulled out on day 2. Four drains/catheters were then placed to apply HIPEC to the abdomen. The abdomen was permanently closed with anatomical plans. HIPEC (41°C) was applied with a chemotherapy solution (130 mg irinotecan and 200 mg oxaliplatin) prepared for 60 minutes (Honoré C et al., 2017). During the procedure, the temperature of the delivered fluid, intraperitoneal temperature and body temperature were monitored. The body temperature was 36.5-37°C. No complications were observed in the patient, who was closely followed in the intensive care unit during the postoperative period for 1 night. Therapeutic options for patients with advanced disease are limited. There are data in the literature suggesting that sunitinib may be associated with clinical benefit, even in previously treated patients (Italiano et al., 2013). The patient was discharged 6 days after surgery and was prescribed a tyrosine kinase receptor inhibitor (sunitinib maleate). The disease recurred. The patient died 8 months later because of progressive disease.

3. Discussion

A DSRCT, first described in 1989, is a rare sarcoma that is difficult to diagnose because of its low incidence in the general population (Gerald et al., 1995). No more than 300 cases have been reported in the literature. This aggressive malignancy is usually found in paediatric and young adult patients, with a male:female ratio of 3:1. The age range of 73% of cases is 10–16 years (Jellouli et al., 2003).

The cells from which these tumours originate are unknown. However, DSRCT is frequently found on the mesothelial-coated surface, which is thought to be the origin. DSRCT usually arises from the abdominal or pelvic peritoneum and very rarely from the head and neck, base of the skull, paratesticular region, ovary, brain and internal thoracic organs (Biswas et al., 2005). Clinical manifestations are usually non-specific; the tumour does not present any symptoms until there is evidence of compression in surrounding structures or extensive invasion. Patients are diagnosed during the stage of extensive DSRCT progression. Symptoms include abdominal distress/distension, abdominal pain, weight loss or changes in bowel habits (Biswas et al., 2005).

The most characteristic imaging feature of abdominal DSRCT is not pathognomonic, with single or multiple lobular peritoneal soft tissue masses that are not derived from a specific organ (Pickhardt et al., 1999).

The diagnosis of DSRCT is difficult because of similar morphological manifestations in other small round cell tumours, such as Ewing's sarcoma, rhabdomyosarcoma, primitive neuroectodermal tumour, neuroblastoma and Wilms tumour (Ordóñez, 1998). Mutual translocation t(11; 22)(p13; q12) resulting in EWS–WT1 gene fusion has recently been reported as specific to DSRCT (Stuart-Buttlea et al., 2008).

Despite the search for a wide variety of therapies, there has been no dramatic improvement in the overall survival of patients with DSRCT. Treatment alternatives for abdominal DSRCT are not well documented because of the rarity of the disease. Due to the aggressiveness of the disease, DSRCT treatment relies on multimodal therapies, including comprehensive surgery when available, abdominal radiotherapy or systemic chemotherapy without abdominal radiotherapy (Stuart-Buttlea et al., 2008). The combination of these three methods showed better results compared with each method separately. The overall response rate was 39%, and the survival rate at 3 years was approximately 50% (Biswas et al., 2005; Stuart-Buttlea et al., 2008).

Despite surgical intervention, radiotherapy and multi-drug chemotherapy, the prognosis of DSRCT is poor (Bellah et al., 2005; Hiralal et al., 2007; Honoré et al., 2017). In recent years, chemotherapy regimens have been reported to extend the median survival by approximately 17 months (Lal et al., 2005; Stuart-Buttlea et al., 2008). In addition, percutaneous stenting (biliary) has also been reported in paediatric and adult cases to prolong life span and enhance comfort (Irwin et al., 2004). The effect of cytoreductive surgery on survival is unclear. Some authors suggest an improvement in survival for operative versus non-

operative tumours, with a median survival of 34 months versus 14 months, respectively (Biswas et al., 2005). Lal reported a significant effect of surgery on overall survival, with a 3-year survival rate of 58% compared with 0% in patients with unresectable disease. The surgical benefit is greater after complete resection, but this course of action is not always possible because of the widespread extent of the disease (Lal et al., 2005).

There are only a few reports on the use of chemotherapy for DSRCT. Multiagent chemotherapy leads to an approximately 40% reduction in tumour size (Biswas et al, 2005; Stuart-Buttlea et al., 2008). Chemotherapy may be beneficial for DSRCT patients; however, disease recurrence often occurs within 6 months (Lauridant-Philippin et al., 2010). Data on the use of radiation therapy for DSRCT are limited. This approach is primarily intended to destroy residual disease or relieve symptoms. Therapeutic use is limited by peritoneal spread to intra-abdominal organs and sensitivity to radiation (Jellouli et al., 2003; Stuart-Buttlea et al., 2008).

A recently used approach is multimodal therapy such as hyperthermia intraperitoneal chemotherapy. Conflicting findings have been reported from studies involving very few cases. In a series of seven adults treated with cytoreductive surgery and HIPEC, overall survival did not improve significantly (Gil et al., 2004). In a retrospective review, Hayes Jordan found shorter recurrence-free survival in patients with than in those without HIPEC (5.85 versus 8.85 months), but this difference was not statistically significant due to the low number of patients. A better outcome in paediatric patients was observed (Hayes-Jordan et al., 2010). For this reason, more patients need to be evaluated to determine the efficacy of HIPEC in DSRCT.

Complete resection of multiple intra-abdominal tumour implants is sometimes achieved by CRS and HIPEC, followed by hyperthermia chemotherapy at approximately 41 °C for a period of time. HIPEC may provide microscopic control of abdominal DSRCT after surgical resection and prevent, or prolong the time to recurrence (Msika et al., 2010).

Despite multimodal treatment, including CRS, neoadjuvant and adjuvant chemotherapy and radiotherapy, the mean 5-year survival rate in the majority of reported series is < 25%. Although the advantages of HIPEC after CRS are not absolutely known in these patients, HIPEC-associated CRS is being used as a new approach in paediatric patients (Reingruber et al., 2007).

HIPEC for adults is now a well-known procedure performed by experienced teams. Although there are studies related to HIPEC conducted in adults in Turkey, HIPEC has not been reported in paediatric patients. This procedure provides a local alternative approach to systematic treatment. Current observations and recently published articles suggest that CRS and HIPEC are practical procedures used in a multidisciplinary approach in paediatric patients. However, as there is insufficient experience and knowledge about implementing CRS and HIPEC in paediatric patients, this procedure should be used only after CRS.There is no more treatment option for patients with recurrent advanced disease. Our patient also survived 8 months after the HIPEC procedure. The experience of a small number of adult patients is similar with the average life expectancy. There is even less experience with this treatment option in pediatric patients.

In summary, HIPEC can be applied in paediatric patients for the treatment of resistant DSRCT. However, the benefit of HIPEC is still unknown and should be evaluated in a prospective trial. Further prospective studies are needed along with molecular analyses of DSRCT to determine a specific targeted treatment.

The authors declare no conflicts of interest.

REFERENCES

Bellah, R., Suzuki-Bordalo, L., Brecher, E., Ginsberg, J.P., Maris, J., Pawel, B.R., 2005. Desmoplastic small round cell tumor in the abdomen and pelvis: Report of CT findings in 11 affected children and young adults. AJR Am. J. Roentgenol. 184, 1910-1914.

Biswas, G., Laskar, S., Banavali, S.D., Gujral, S., Kurkure, P.A., Muckaden, M., Parikh, P.M., Nair, C.N. 2005. Desmoplastic small round cell tumor: Extra abdominal and abdominal presentations and the results of treatment. Indian J. Cancer. 42, 78-84.

Gerald, W.L., Rosai, J., Ladanyi, M. 1995. Characterization of the genomic breakpoint and chimeric transcripts in the EWS-WT1 gene fusion of desmoplastic small round cell tumor. Proc. Natl. Acad. Sci. 14, 1028-1032.

Gerald, W.L., and Rosai, J., 1989. Case 2 desmoplastic small cell tumor with divergent differentiation. Pediatr. Pathol. 9, 177-183.

Gil, A., Portilla, G.A., Brun, Sugarbaker., P.H., 2004. Clinical perspective on desmoplastic small round cell tumour. Oncology, 67, 231-242

Hartmann, C., Weinel, P., Schmid, H., Grigull, L., Sander, A., Linderkamp, C., Welte, K., Reinhardt, D., 2011 Oxaliplatin, Irinotecan, and Gemcitabine: A novel combination in the therapy of progressed, relapsed, or refractory tumors in children. J. Pediatr. Hematol. Oncol. 33, 344-349.

Hayes-Jordan, A., Green, H., Fitzgerald, N., Xiao, L.C., Anderson, P., 2010. Novel treatment for desmoplastic small round cell tumor: Hyperthermic intraperitoneal perfusion. J. Pediatr. Surg. 45, 1000-1006.

Hiralal, G.S., Thulkar, S., Rao., S.K., 2007. Desmoplastic round cell tumour of the abdomen. Singapore Med. J. 48, e19-21.

Honoré, C., Atallah, V., Mir, O., Orbach, D., Ferron, G., LePéchoux, C., Delhorme, J.B., Philippe-Chomette, P., Sarnacki, S., Msika, S., Terrier, P., Glehen, O., Martelli, H., Minard-Colin, V., Bertucci, F., Blay, J.Y., Bonvalot , S., Elias, D., LeCesne, A., Sargos., P., 2017. Abdominal desmoplastic small round cell tumor without extraperitoneal metastases: Is there a benefit for HIPEC after macroscopically complete cytoreductive surgery? PLoS One. 12, e0171639.

Irwin, G.J., Mac Lennan, A.C., Carachi, R., 2004. Interventional radiology cases from the Royal Hospital for Sick Children, Glasgow: Percutaneous metal biliary stent placement for palliation of intraabdominal desmoplastic small round cell tumour in a child. Eur. J. Pediatr. Surg. 14, 130-132.

Italiano, A., Kind, M., Cioffi, A., , Bui, R.G.B., 2013. Clinical activity of sunitinib in patients with advanced desmoplastic round cell tumor: A case series. Target Oncol. 8, 211-213.

Jellouli, M., Mekki, M., Krichene, I., Zakhama, A., Belghith, M., Jouini, R., Sahnoun, L., Rammeh, S., Harbi, A., Nouri, A., 2003. Intra-abdominal desmoplastic small round cell tumor in childhood: Case report and review of the literature. Bull Cancer. 90, 1063-1066.

Kim, J.W., Park, J.H., Cho, H.J., Kwon, J.H., Koh, Y., Kim, S.J., Kim, S.H., Lee, S.H., Im, S.A., Kim, Y.T., Kim, W.H., 2009. A case of desmoplastic small round cell tumor diagnosed in a young female patient. Cancer Res. Treat. 41, 233-236

Lal, D.R., Su, W.T., Wolden, S.L., Loh, K.C., Modak, S., La, Quaglia, M.P., 2005. Results of multimodal treatment for desmoplastic small round cell tumors. J. Pediatr. Surg. 40, 251-255.

Lauridant-Philippin, G., Ledem, N., Lemoine, F., Gouerant, S., Guillemet, C., Michel, P., Scotte, M., Di, Fiore, F., 2010. Optimal treatment with systemic chemotherapy, complete surgical excision and hyperthermic intraperitoneal chemotherapy for a desmplastic small round cell tumor in an adulte male patient. Gastroentérologie Clinique et Biologique. 34, 321-324.

Msika, S., Gruden, E., Sarnacki, S., Orbach, D., Philippe-Chomette, P., Castel, B., Sabaté, J.M., Flamant, Y., Kianmanesh, R., 2010. Cytoreductive surgery associated to hyperthermic intraperitoneal chemoperfusion for desmoplastic round small cell tumor with peritoneal carcinomatosis in young patients. J. Pediatr. Surg. 45, 1617–1621.

Ordonez, N.G., 1998. Desmoplastic small round cell tumor: I: A histopathologic study of 39 cases with emphasis on unusual histological patterns. Am. J. Surg. Pathol. 22, 1303-1313.

Pickhardt, P.J., Fisher, A.J., Balfe, D.M., Dehner, L.P., Huettner, P.C., 1999. Desmoplastic small round cell tumor of the abdomen: Radiologic-histopathologic correlation. Radiol. 210, 633-638.

Reingruber, B., Boettcher, M.I., Klein, P., Hohenberger, W., Pelz, J.O., 2007. Hyperthermic intraperitoneal chemoperfusion is an option for treatment of peritoneal carcinomatosis in children. J. Pediatr. Surg. 4, 17-21.

Stuart-Buttlea, C.E., Smarta, C.J., Pritchardb, S., Martinc, D., Welcha, I.M., 2008. Desmoplastic small round cell tumour: A review of literature and treatment options. Surg. Oncol. 17, 107-112