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THE EFFECT OF MUSIC ON HEART RATE VARIABILITY (REVIEW)

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Abstract

Music therapy and the use of music in medical practice have now become rapidly advancing and promising areas of non-invasive alternative medicine. However, the opinions of physicians and therapists on the implementation of this complementary therapy, especially in the process of treating the patient, are constantly different. In addition, the effect of music and individual methodological procedures are not uniform and defined in detail. Therefore, this review study summarizes the results and conclusions of some selected high-quality publications over the last decade and makes suggestions for improvement and further research. It focuses mainly on the evaluation of changes in heart rate variability (HRV) as an indicator of the activity of the autonomic nervous system (ANS) in connection with the application of music in the process of passive music therapy.

Keywords: music therapy, heart rate variability, review article

"Music is a cure for the suffering of the soul."
Quintus Flaccus Horatius

INTRODUCTION

Music, known as an art form for thousands of years, has become an integral part of modern human life. Thanks to electronic devices free-available on the market we are in contact with music practically every day in different places. There are countless songs of different musical genres and styles. It is already well-known that listening to music subjectively affects not only our emotions and feelings but also higher feelings, moods, and affections. The overall mental balance of an individual thus plays a major role in the aspect of his health.

Modern medicine today prefers an individual, highly specific approach to the patient. With the development of a wide range of diseases of civilization, other diseases and disabilities, non-invasive medicine, in the form of various complementary therapies, has gradually found a place in the process of diagnosis and treatment.

A relatively unexplored area is music therapy, the so-called music therapy. Stimulation of the auditory system with music is gaining more and more attention in the treatment and prevention of disorders (1). According to the currently available evidence in individual studies, music in the individual primarily attracts attention, can suppress a number of emotions, changes or regulates mood, increases work performance, stimulates arousal, induces the

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functioning of higher nervous functions, regulates inhibitions, supports rhythmic movement, and others (1). Musical auditory stimulation, thus, evokes a diverse range of psychological and hemodynamic expressions by influencing the autonomic regulation of cardiac activity.

The autonomic nervous system is the main regulatory system that ensures flexibility, homeostasis, and adaptability of the body during rest but also in stressful situations. Its centers are located in the cortical (cerebral cortex) and subcortical areas (spinal cord, brain stem, hypothalamus, etc.) and its activity in general cannot be controlled by will. From a functional point of view, it consists of two units: pars sympathica and pars parasympathica, which in principle work antagonistically. This system is involved in the management and control of all vital processes (internal organ activity, homeostasis, smooth muscle function, heart and gland function, metabolism, and vital physiological functions) (2).

Heart rate variability is considered to be one of the most important indicators of autonomic regulation of heart function in the literature. Even in a normal ECG recording, it can be noticed that the time intervals between R-R oscillations are variable. We observe rhythmic oscillations in the heart rhythm. Heart rate variability (HRV) is thus a mirror of the cardiorespiratory control system and is a manifestation of beat-to-beat regulation of the heart pacemaker (Javorka, 1996). The heart rate itself is thus influenced by the activity of the autonomic nervous system and its effect on the sinoatrial node. In simple terms, the overall reduction in HRV is an indicator of poor cardiovascular function, e.g. as in chronic heart failure, while an increase in HRV corresponds to an improvement in cardiovascular function. The HRV analysis method has gradually gained attention for its potential to detect abnormal physiologies.

Musical sound stimulation affects HRV through a neural mechanism that is not yet exactly known (1, 4).

In addition, many previous studies have suggested that music therapy has positive effects on HRV in sick patients. However, therapeutic procedures and methods are not uniform and the influence of music is not clear. That is why the opinions of therapeutic specialists and doctors on musical stimulus differ. Clarification of physiological reactions associated with music is an important step for the development and future of music therapy as one of the therapeutic or preventive therapies, for example in the field of cardiovascular disorders. The current insufficient number and quality of studies does not make it possible to unambiguously determine when and under what conditions music therapy is therapeutically effective (5,6).

Therefore, this review study will focus on the analysis of existing data in relation to the effects of music on HRV in the concept of music therapy

METHODS

The review study consists of full-text articles that were searched in web of science databases via the kopernio application. The kopernio interface collects scientific publications and collaborates with more than 20,000 databases. The articles were searched and selected according to the required criteria within the period from September to October 2020. The keywords music therapy and central nervous system, HRV, and music therapy were searched for priority for selection. On the basis of abstracts and titles, the articles that were not directly related to the topic were excluded, resp. heart rate variability was not examined as a priority as an indicator of ANS activity. References in individual publications for the expansion of electronic search were also independently checked on an ongoing basis.

Review articles and studies that did not contain an abstract or did not provide a complete text in English were excluded. Another criterion in the selection was the time classification of individual publications. Priority was given to basic and clinical studies within the period between 2010 and 2020 which investigated the above-mentioned effect of sound auditory stimulation in connection with the autonomic nervous system.

RESULTS

More than 3,190 links related to music therapy and the central nervous system and approximately 17,300 links in music therapy and heart rate variability were found in the electronic search after entering key terms and time parameters. In the second round of the selection, articles and books that were not clearly related in content to the subject of the search for the review study were eliminated. After individual consideration, the titles and abstracts of 45 articles were subjected to a final analysis and a final selection. A search of the list of references for some publications confirmed the absence of relevant documents and, therefore, such work was also excluded. After a highly specific selection a total of 30 most relevant and interesting articles from the last decade were selected for a final processing. A brief overview of selected conclusions of some studies is collected in Tab.1.

Author and year	Conclusions
Orita et al., 2012 (7)	The authors showed that music therapy suppressed parasympathetic nervous activities and can trigger the dominant state of sympathetic nervous activities in patients with severely and multiply disabled children and that the frequency domain analysis of HRV could be a powerful tool for the objective evaluation of music therapy.
Martiniano et al., 2017 (8)	Musical auditory stimulus intensified HR autonomic responses to anti-hypertensive medication in well-controlled hypertensive subjects.
Chih-Yaun Chuang et al., 2010 (5)	This study provides a preliminary evidence that music therapy may be clinically useful for promoting relaxation sensation and increasing parasympathetic nervous system activity in treated cancer survivors.
Raglio et al., 2015 (9)	In conclusion, a more methodological rigor and a clear definition of music approaches are needed to improve the quality of music therapy research and to focus on the specific role of music-based interventions in psychological symptoms in the field of neurology.
Ziya Tan et al., 2015 (10)	The authors showed and emphasized that, as in other studies, the heartbeat and HRV of patients (n=50) listening to a music sample of their own choice during scintigraphy were significantly lower than in the control group (without music).
Ribeiro et al., 2018 (11)	Music therapy had a significant and positive impact on anxiety and depression, acting on prevention of cardiovascular diseases.
Archana et al., 2016 (12)	This study provides a preliminary evidence that listening to preferential music could be an effective method of relaxation, as indicated by a shift of the autonomic balance towards the parasympathetic activity among medical students.
Roque at. al., 2013 (13)	We suggest that relaxant baroque and excitatory heavy metal music slightly decrease global heart rate variability because of the equivalent sound level.
Amaral et al., 2016 (1)	The researchers focused on different intensities of baroque and heavy metal music in connection with the heartbeat. They noted that heavy metal and baroque musical auditory stimulation at lower intensities acutely reduced global modulation of the heart and only heavy metal music reduced HRV at higher intensities. They may surmise that HRV elicited by high intensity heavy metal music was elicited by an autonomic response involved in the acoustic startle reflex.

Silva at al., 2014 (14)	The findings of the present study showed that acute exposure to classical baroque music reduced the sympathetic modulation of the heart, while excitatory heavy metal music decreased the global variability of the heart rate. Moreover, the classical baroque music acutely increased HRV in healthy male subjects.
Koelsch et al., 2015 (16)	Music is potentially a low-cost and safe adjuvant for intervention and therapy. However, the effects of music on the heart rate are small and results of studies on this topic are often inconsistent.
Trappe et al., 2016 (17)	Music by Mozart and Strauss lowered the subjects‘ blood pressure and heart, while music by ABBA did not. Mozart’s music had the strongest effect, the piece used was his Symphony No. 40 in G minor (KV550).

DISCUSSION

It is an indisputable fact that music has gradually found its way and application in the field of medicine. We are talking about so-called music therapy as a form of non-invasive approach to the patient. The main goals of therapists in the broadest spectrum are to encourage the patient to express and release their own emotions, to help with stress or anxiety situations associated with everyday life or directly with the diagnosis, to improve mood and, finally, the overall quality of life. As Javorka et al. noted, in addition to the well-known regular physical exercise and sport, various relaxation methods as well as slow breathing training associated with music therapy have been used for a long time in autonomic as well as emotional dysfunction, as well as in the treatment of pain, anxiety symptoms, and other conditions (19).

Surveys point to the fact that the patient does not need skills or talent in the field of music in order to benefit from music (20). Therefore, it is possible to divide the music therapy approach into passive or active. In this review study we selected articles that examine the impact of music on a person who is a passive object for the application of music and does not perform any active activity in connection with the composition or the creation of musical sounds.

Over the last decade hundreds of „...articles pointing to a great importance of using music in connection with healthy and, above all, especially sick patients have been published. However, these individual publications are very diverse, limited (insufficient number of patients, gender, age, absence of control groups), non-specific in terms of methodological approach, selection, application and effects of individual musical patterns and their analytical description. It is necessary to examine in more detail and then clearly define qualitatively and quantitatively the effect of music on humans for repeatability and increase the credibility of music therapy in medical practice for specific cases. Therefore, one of the most important criteria in the selection of the study was to evaluate the effect of music on humans in connection with the examination of a physiological parameter HRV. This appears in several literature as an important quantifiable indicator of the activity of the autonomic nervous system associated with general homeostasis. It should be noted that this parameter also has its limitations, which need to be comprehensively considered in the evaluation and presentation (RSA, humoral effects, baroreflexes, pharmacological profile, current patient status, etc.).

After studying the particular publications we can say that in all the collected studies there were significant or less significant oscillations of the heart rhythm when listening to music, which were subsequently evaluated most often by the method of frequency analysis (HF, LF, HF/LF). HRV frequency analysis is currently the simplest non-invasive tool for investigating the sympathetic and parasympathetic contribution to overall autonomous management (21).

A decrease in HRV with a decrease in the activity of the high-frequency component is observable in several physiological as well as pathological situations. Examples are persons with insufficient movement at work, with minimal physical activity, patients with essential hypertension, after myocardial infarction, with diabetes mellitus, and others (19).

After the analysis of the results (LF / HF, RR interval, geometric indices RRTri, SD1, SD2, SD1 / SD2), after considering the limitations, it can be generally concluded that listening to music is clinically useful mainly in promoting relaxation, fatigue reduction, and elimination of depression as evidenced by individual studies that indicated an increase in the activity of the parasympathetic nervous system, e.g. in patients treated for cancer or in mothers of premature babies. (5, 11, 25). Also interesting is the result of studies that showed a more intense effect of antihypertensive drug treatment on the heart rate in connection with music, even after taking into account that the resting heart rate was already reduced by listening to music (8). It is evident that the influence of music on HRV cannot be denied (Table 2). Also Leubner et. al reported in their 2017 survey study a statistically significant reduction in the degree of depression in patients, always compared to the control group. Using the right method and music literally "trained the parasympathetic," thereby relieving stress, improving hypertension, chronic fatigue, irritable bowel syndrome, and other conditions (22).

Table 2 Percentage of individual types (genres) of music samples in the collected studies and their impact on HRV (positive ↑, negative ↓) evaluated on the basis of its frequency analysis

	percentage (%)	*HRV change*
metal vs. classical	25	↓ ↑
noise	15	↓
music specifc frequency (f)	15	depands on f
instrumental (no singning)	15	↑
pleasant, soft, relaxing	30	↑
not specified own choice	5	↑

A relatively frequent limitation of individual studies appears to be a small number of examined individuals, the absence of control groups, or age representation. On the other hand, a significant shift in modern research and music therapy, which is again confirmed by individual publications, is the integration of women during hormonal instability, emotional profile, and other sexual specifics in connection with the observation of heart rate variability. The literature speaks of various cardiovascular and physiological responses when comparing men and women not only in general but also in connection with music therapy (1). Intense stress responses to auditory stimulation were observed in women as in men, and other studies have been conducted on emerging differences in psychophysiological responses due to current hormonal status. Due to the exclusion of the influence of the interference of the follicular and luteal phases of the cycle of women on the autonomic regulation of the heart, it is recommended not to perform the examination within the period between 10^{th}–15^{th} and 20^{th}–25^{th} day of the cycle at which the basic non-linear properties of HRV are affected (1). However, research addressing these differences is still insufficient at present. A comparison of the gender distribution from all collected studies where information was available can be seen in Tab. 3.

Table 3 Age composition and classification based on gender and health status (± SD)

	n	%	healthy	unhealthy	total	MIN age	MAX age
Male	167	30					
Female	301	55	374	178	552	22.67±10	44.16±24
not divided	84	15					

Our review study shows an increased number of women in passive music therapy research over the last 10 years. We consider this information useful for objectifying the overall results and further studies. Furthermore, more than 67% of the examined individuals were healthy, it means they did not suffer from any known cardiac dysregulation, functional disorders, acute or chronic diseases that would potentially affect HRV. In addition, healthy probands did not take any drugs and according to the BMI index did not fall into the group of obese or malnourished. Such a group of individuals is considered in several studies to be the most appropriate starting point for clarifying the principle of the degree of influencing the balance of ANS by music, taking into account the appropriate age (early adulthood is the most appropriate).

A great variety of individual studies included in this review is observed in the area of musical stimulus selection. The genre, tempo, volume, duration of the music samples and the methods of the investigation protocol are quite different. HRV is most often observed in the application of two generally different music groups, the effect of "exciting" and, on the other hand, "calming" music in connection with the phases of silence. Koelsch et al. (2015) noted that the same musical stimulus can have both stimulating and relaxing-suppressing effects (16). For example, even at the level of the brainstem, metal beats can provoke stimulating autonomous reactions, while the same composition, on the other hand, has a calming effect on the metal enthusiast (after considering endocrine and immune changes) (1).

In addition, one of the last interesting discoveries is so-called "Mozart effect". According to several Canadian studies the increase in IQ when listening to or playing classical music is valid not only for general but also for spatial intelligence. Dr. Rauscher thus perceives music in her work as a gateway to higher brain functions and is convinced that the "right" music can help us understand the work of the brain, while also positively influencing thinking and creation (23, 24, 26).

The selection and specification of a music track for a music therapy protocol and a particular individual appear to be very important. Amaral et al. in his study emphasized the importance of subjective composition selection and subsequent caution in interpreting the results obtained, as he noted a diversity in selection in other studies as well. He states that the patients' choice of preferred sedative music resulted in increased dopamine release in the brain's compensatory areas (nucleus accumbens, nucleus caudatus) (1, 13).

Furthermore, in the analysis of data and interpretation of the effect of music on humans there is an insufficient physical description of the applied music sample in individual research. Although frequency or time analysis of HRV is the main indicator of ANS in several publications, its changes and association with specific intensities, frequencies, noise, tempo, and duration have not been clarified yet. An interesting and little-explored area is, for example, the influence of music intensity or specifically defined frequencies on HRV and, thus, on ANS. Lee et al. observed a significant interaction between sympathetic cardiac regulation and white noise intensity - the higher the white noise intensity, the higher the LF / HF ratio and the lower the HRV (26, 27). Aravena et al. (2019) observed a significant reduction in the degree of anxiety and fear, as well as a reduction in salivary cortisol levels in patients who underwent tooth extraction while listening to a music track at 432 Hz compared to the controls (18).

Next, we present the recommendations and suggestions for the methodological protocol summarized in the points.

- When choosing a musical stimulus for research, allow the individual to choose their own musical stimulus from several pre - prepared musical genres (baroque, metal, jazz, etc.)
- Musical stimuli or a group of stimuli must be clearly characterized in terms of musical, acoustic, and emotional influence (tempo, genre, musical performance, intensity, duration, spectral analysis, power spectral density, frequencies, subjective emotional perception – feeling of excitement / relaxation, etc.)
- Detailed history and description of the individual (BMI, age, sex, health status, etc.)
- Inclusion of control groups in clinical trials with a control stimulus with as many control stimuli as possible
- Inclusion and evaluation of psychological variables (mood / anger / anxiety)
- In patients examined, implement often missing data, e.g. about the length of hospitalization, overall patient satisfaction, intake of sedatives, opioids, and other drugs
- Description of the number and repetition of music therapy meetings in a time scale
- In addition to HRV, consider incorporating ANS-related emotional valence testing, for example, using electrodermal activity measurements, and further integrate voluntarily modified respiration control
- Application of music track, stimulus, samples in an acoustically isolated room
- High-quality comfortable hardware music components (headphones, etc.) and a comfortable position for the patient

CONCLUSION

Any further study dealing with the application of music to humans and the subsequent observation and evaluation of cardiovascular parameters appears to be very important and useful. In further observation and evaluation of cardiovascular parameters in the process of music therapy, we recommend including a detailed description of the methodological procedure (mainly selection and definition of music sample, current health status of the proband, definition of restrictions, control group, etc.). Music therapy, passive or active, can thus become a recognized and other undisputed therapy and more applied in current medical practice.

REFERENCES

1. Amaral J, Guida HL, Abreu LC, et al. Effects of auditory stimulation with music of different intensities on heart period. Journal of Traditional and Complementary Medicine 2016; 6: 23-28.
2. Slavikova M, Sekaninova N, Bona OL, et al. Biofeedback – A promising non-pharmacological tool of stress – related disorders. Acta medica martiniana 2020; 20(1):1-8.
3. Javorka K. Clinical physiology for pediatricians (in Slovak). Martin: Osveta; 1996. 487p.
4. Valenti VE, Guida HL, Frizzo ACF, et al. Auditory stimulation and cardiac autonomic regulation. Clinics 2012; 67(8):955-958.
5. Chuang CY, Han WR, Li PC, et al. Effects of music therapy on subjective sensations and heart rate variability in treated cancer survivors: a pilot study. Complement Ther Med. 2010; 18(5): 224-6.
6. Chuang CY, Han WR, Li PC, et al. Effect of long-term music therapy intervention on autonomic function in anthracycline-treated breast cancer patients. Integrat Cancer Ther 2011; 10(4): 312-6.
7. Orita M, Hayashida N, Shinkawa T, et al. Monitoring the autonomic nervous acitivity as the objective evaluation of music therapy for severely and multiply disabled children. Tohoku J.Exp. Med 2012; 227: 185-189.
8. Martiniano EC, Santana MDR, Barros ELD, et al. Musical auditory stimulus acutely influences heart rate dynamic responses to medication in subjects with well-controlled hypertension, Scientific reports 2018; 8:958.

9. Raglio A, Attardo L, Gontero G, et al. Effects of music and music therapy on mood in neurological patients. World journal of psychiatry 2015; 5(1): 68-67.
10. Tan ZY, Ozdemir S, Temiz A, et. al. The effect of relaxing music on heart rate and heart rate variability during ECG Gated-myocardial perfusion scintigraphy. Complementary therapies in clinical practice 2015; 21: 137–140.
11. Ribeiro MKA, Alcantara-Silva TRM, Oliveira JCM, et al. Music therapy intervention in cardiac autonomic modulation, anxiety, and depression in mothers of preterms: randomized controlled trial. BMC psychology 2018; 6-57.
12. Archana R, Mukilan R. Beneficial effect of preferential music on excercise induced changes in heart rate variability. Journal of clinical and diagnostic research 2016; 10(5): 9–11.
13. Roque AL, Valenti VE, Guida HL, et. al. The effects of auditory stimulation with music on heart rate variability in healthy women. Clinics 2013; 68(7): 960–967.
14. Silva SAF, Guida HL, Antonio AM, et al. Acute auditory stimulation with different styles of music influences cardiac autonomic regulation in men. International cardiovascular research journal 2014; 8(3): 105-110.
15. Thakare AE, Mehrotra R, Singh A. Effect of music tempo on exercise performance and heart rate among young adults. Int J Physiol Pathophysiol Pharmacol 2017; 9(2): 35-39.
16. Koelsch S, Jäncke L. Music and the Heart. European heart Journal 2015; 36: 3043-3048.
17. Trappe HJ, Voit G. The cardiovascular effect of musical genres. Deutsches Arzteblatt International 2016; 113: 347-52.
18. Aravena PC, Almonacid C, Mancilla MI. Effect of music at 432 Hz and 440 Hz on dental anxiety and salivary cortisol levels in patients undergoing tooth extraction: a randomized clinical trial. Journal of applied oral science 2020; 28: e20190601.
19. Javorka K. et al. Heart rate variability (in Slovak). Martin: Osveta; 2008. 204p.
20. Wong C. The benefits of music therapy. Verywell mind, 2018. Available: https://www.verywellmind.com/benefits-of-music-therapy-89829?print.
21. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation 1996; 93(5):1043-65.
22. Leubner D, Hinterberger T. Reviewing the effectiveness of music interventions in treating depression. Frontiers in Psychology 2017; 8: 1109.
23. Campbell D. Mozartuv efekt. Eminent; 2008. 271p.
24. Hally T. The Mozzart effect. Mensa international Journal 2008; 525.
25. Idrobo-Ávilla EH, Loaiza-Correa H, Noorden L, et al. Different types of sounds and their relationship with the electrocardiographic signal and the cardiovascular system-review. Frontiers in Physiology 2018; 9:525.
26. Lin LC, Lee MW, Wei RC, et al. Mozzart K.448 listening decreased seizure recurrence and epileptiform discharges in children with first unprovoked seizures: a randomized controlled study. BMC complement alter med. 2014; 14:17.
27. Turpin G, Siddle DA. Cardiac and forearm plethysmographic responses to high intensity audiotory stimulation. Biol psychol 1998; 6: 267-281.
28. Chen SC, Yeh ML, Chang HJ, et al. Music, heart rate variability, and symptom clusters: a comparative study. Supportive care in cancer 2020; 28: 351-360.

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CORRELATION OF INCREASED TOTAL SERUM IMMUNOGLOBULIN E LEVELS AND HIDRADENITIS SUPPURATIVA

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Abstract

Introduction: Hidradenitis suppurativa is a chronic inflammatory skin disease with a typical formation of inflamed nodules, abscesses, and sinus tracts usually in the axillary, inguinal, and anogenital region. We decided to investigate the possible association of hidradenitis suppurativa and total IgE elevation and to explore the patients' characteristics which can be related to high IgE levels.

Methods: We performed a retrospective observational study which included 67 patients with moderate-to-severe stage of hidradenitis suppurativa followed up in our outpatient dermatology department. Total IgE, IgA, IgG, IgM, and CRP serum levels were measured. A personal and family history was taken. We asked them about allergic diseases and cigarette smoking and determined the basic parameters such as the weight and height of the patients.

Results: Elevated total IgE levels were noticed in 21 patients (31.3%), of which 6 had a history of allergic disorder. Three of them had allergic rhinoconjunctivitis and the other three were suffering from atopic dermatitis. The mean total IgE level was 203.0 IU/ml with a maximum value of 1,954 IU/ml. Analysis of the factors, such as cigarette smoking, sex, elevated CRP, body mass index, and the number of affected areas, did not show an association with increased IgE levels.

Conclusion: Our study showed a higher mean value of total IgE in patients with moderate to severe hidradenitis suppurativa than in the general population. However, we did not confirm an association with any characteristics of the patients. Limitations of this work include a small number of patients and a lack of the control group, therefore further and more extensive studies are needed to support these results.

Key words: Hidradenitis suppurativa, acne inversa, immunoglobulin E

INTRODUCTION

Hidradenitis suppurativa (HS), also known as acne inversa, is a chronic, recurrent inflammatory skin disease. It usually manifests with painful, deep-seated, inflamed lesions in the axillary, inguinal, and anogenital regions. Depending on the stage of the disease, the nodules, abscesses, fistulas, sinus tracts, and scars are formed (1). The prevalence rates range between 1% to 4% in European countries and women are more frequently affected than men with a sex ratio of 3:1 (2,3). However, new studies showed that men are suffering from severe HS more often than women (4). It occurs usually after puberty, mostly in the second decade of life (3). There are several phenotypes distinguished in HS, each of them has different severity and clinical manifestation (4). We know HS is associated with the disorders of follicular occlusion: acne conglobata, sinus pilonidalis, and dissecting cellulitis of the scalp, but connections with many other diseases are studied (5). The prognosis of HS depends on the intensity of the disease, but also on how early it is diagnosed and the therapy is set. To determine an adequate treatment, the pathogenesis of the disease needs to be elucidated.

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In past, HS was thought to be an infectious disease of apocrine glands, but concepts on HS have changed over time. Nowadays, the follicular occlusion is considered the main pathogenetic mechanism followed by a secondary bacterial infection. It is assumed that the disease is triggered in a genetically predisposed individual by an environmental insults or internal factors, such as mechanical friction, cigarette smoking, obesity, and hormonal abnormalities (6,7).

Recent findings suggest that HS should be viewed as a systemic inflammatory disease because of dysregulated immune response which leads to elevated levels of proinflammatory cytokines IL-1β (Interleukin), TNF-α (Tumour Necrosis Factor), and IL-10 in HS skin at even greater levels than in psoriatic skin and the elevation of cytokines was also find in the serum of the patients (8). We decided to investigate the possible association between elevated IgE and HS and to explore the patients' characteristics which can be related to high IgE levels.

METHODS

Patients with moderate to severe HS - PGA (Physician Global Assessment) stage from 3 to 5 followed up at our outpatient dermatology department from February 2015 to October 2020 were included in our study. Total IgE, IgA, IgG, and IgM serum levels as well as the inflammatory parameter CRP were measured in these. A personal and family history was taken. We searched whether these patients suffer from allergic diseases and smoke cigarettes. We also determined the basic parameters such as the weight and height of the patients. A single T-test was used for data analysis. A P-value <0.05 was considered as statistically significant. Total IgE was considered elevated if it was above the laboratory's upper normal level (>100 IU/ml). The control study group was not established because of a retrospective type of the study and it is currently not possible to set up a control group due to the epidemiological situation.

RESULTS

A total of 67 patients were included in the study. Out of the 67 patients 66% were male, which corresponds to a higher incidence of severe HS forms in men in new studies. The mean age (standard deviation) was 41.9 (±12.9) years and the mean duration of the disease was 15 years. The most commonly affected area was the axillary (79.1%) and inguinal (64%). In one patient, several areas were usually affected. The other affected sites included submammary, sacral, perineal, perianal, and scrotum. Forty-two (62.7%) of the patients were smokers. Twenty patients (29.8%) were overweight. Obesity was noticed in the same number of patients. Sinus pilonidalis was observed in eighteen (26.8%) patients and acne conglobata in eleven (16.4%) patients.

Elevated total IgE levels were noticed in 21 patients (31.3%), of which 6 had a history of allergic disorder. Three of them had allergic rhinoconjunctivitis and the other three were suffering from atopic dermatitis. In our study the mean total IgE level was 203.0 IU/ml with a maximum value of 1,954 IU/ml. Three patients had a concomitant elevation of IgE, IgA, and IgG levels. Total IgG level was elevated in 14 patients, 8 patients had total IgA elevation, and 1 patient had total IgM elevation. Mean total IgE was higher in smokers (P=0.81), in men (P=0.42), and in those with CRP higher than 10 mg/l (P=0.50), but the P-value was not significant for any of these hypotheses. The analysis of other factors (age, body mass index, and the number of affected areas, sinus pilonidalis and acne conglobata) did not show an association with increased IgE levels. We did not investigate the correlation of elevated IgE levels in the HS patients with the most severe PGA stage 5 as this group was very small. Investigated possible characteristics of HS patients associated with total IgE elevation are stated in the following table 1.

Table 1 Possible characteristics of HS patients associated with total IgE elevation

	Total number of patients	Normal IgE n46 (Mean %)	Elevation of IgE n21 (Mean %)
Men	44	27 (58.7%)	17 (81.0%)
Women	23	19 (41.3%)	4 (19.0%)
Smokers	44	30 (65.2%)	14 (66.7%)
Non-smokers	23	17 (37.0%)	6 (28.6%)
CRP elevation	21	14 (30.4%)	7 (33.3%)
Sinus pilonidalis	18	11 (23.9%)	7 (33.3%)
Acne conglobata	11	9 (19.6%)	2 (9.5%)
History of an allergic disorder	17	11 (23.9%)	6 (28.6%)

DISCUSSION

Elevated IgE levels are usually related to atopic diseases, but many other disorders such as helminth infections, immunodeficiency syndromes, and inflammatory diseases are also associated with higher IgE levels (9).

In 2015, a study describing an increase in serum levels of total IgE in about a third (37.4%) of 99 patients with moderate to severe HS was published. Only one patient had a diagnosis of atopic dermatitis and one patient was suffering from asthma. The mean total IgE level was 186.4 IU/ml. Previous studies show that the mean total IgE levels in the general population ranges from 32 to 41 IU/ml (10,11). Higher mean total IgE was in smokers (mean: 238.9 IU/ml vs. 59.4 IU/ml, P=0.02), in men (267.2 IU/ml vs. 103.9 UI/ml, P=0.04), and in those whose HS was not located on the groin (233.8 IU/ml vs. 146.8 UI/ml, P=0.03) (9). In our cohort we did not find a statistically significant association with any of these parameters. However, both studies included moderate-to-severe HS patients and it is a matter of further studies what results would be in cohort of mild-form HS.

To explain a possible association of total IgE elevation and HS, we studied available literature. In HS skin, we know there is an elevation of IL-1β, TNF-α, and IL-10. IL-10 is a major regulatory cytokine of inflammation which is elevated in HS lesions. We found out that IL-10 enhances B-cell differentiation into plasma cells (12). Van der Zee et al, demonstrated a heavy inflammatory infiltrate in chronic HS skin lesions with a marked increase of CD20+ and CD79a+ B cells and CD138+ plasma cells. An increased number of tryptase-positive mast cells were also found in early and chronic lesions and in normal-appearing perilesional skin (13,14). The plasma cells can produce the IgE detected in HS skin and can lead to an increase of IgE in serum. The enhancement of IgE production and infiltration of mast cells in HS skin could trigger a degranulation of these cells, releasing histamine and causing pruritus, a symptom which some HS patients experience (12).

CONCLUSION

Our study showed a higher mean value of total IgE in patients with moderate to severe HS than in the general population. However, we did not confirm an association with any

characteristics of the patients. Limitations of this work include the small number of patients and lack of comparison with a control group, therefore further and more extensive studies are needed to support these results.

REFERENCES

1. Jemec GB. Clinical Practice. Hidradenitis Suppurativa. N Engl J Med 2012; 366 (2): 158-64.
2. Jemec GB, Heidenheim M, Nielsen NH. The prevalence of hidradenitis suppurativa and its potential precursor lesions. J Am Acad Dermatol 1996; 35 (2 pt 1): 191-4.
3. Canoui-Poitrine F, Revuz JE, Wolkenstein P et al. Clinical characteristics of a series of 302 French patiens with hidradenitis suppurativa, with an analysis of factors associated with disease severity. J Am Acad Dermatol 2009; 61 (1): 51-7.
4. Martorell A, Jfri A, Koster SBL et al. Defining hidradenitis suppurativa phenotypes based on the elementary lesion pattern: results of a prospective study. J Eur Acad Dermatol Venereol. 2020; 34(6): 1309-1318.
5. Pecova K. Acne Conglobata Associated with Hidradenitis Suppurativa, Disorders of Follicular Occlusion (Case Report). Acta Medica Martiniana. 2015; 15(2): 30-34.
6. Kurayev A, Ashkar H, Saraiya A, Gottlieb AB. Hidradenitis Suppurativa: Review of the Pathogenesis and Treatment. J Drugs Dermatol. 2016; 15(8): 1017-22.
7. Alikhan A, Lynch PJ, Eisen DB. Hidradenitis suppurativa: a comprehensive review. J Am Acad Dermatol. 2009; 60(4): 539-61.
8. Van der Zee HH, de Ruiter L, van den Broecke DG, et al. Elevated levels of tumour necrosis factor (TNF)-α, interleukin (IL)-1β and IL-10 in hidradenitis suppurativa skin: a rationale for targeting TNF-α and IL-1β. Br J Dermatol 2011;164:1292-8.
9. Pascual JC, García-Martínez FJ, Martorell A, et al. Increased total serum IgE levels in moderate-to-severe hidradenitis suppurativa. Br J Dermatol. 2016; 175(5): 1101-1102.
10. Wittig HJ, Belloit J, De Fillippi I, Royal G. Age-related serum immunoglobulin E levels in healthy subjects and in patients with allergic disease. J Allergy Clin Immunol 1980; 66 (4): 305-13.
11. Hetman S, Kivity S, Greif J, et al. IgE values in the allergic and healthy Israeli population. Ann Allergy 1988; 61 (2): 123-8.
12. Kobayashi N, Nagumo H, Agematsu K. IL-10 enhances B-cell IgE synthesis by promoting differentiation into plasma cells, a process that is inhibited by CD27/CD70 interaction. Clin Exp Immunol 2002; 129 (3): 446-52.
13. Van der Zee HH, de Ruiter L, Boer J, et al. Alterations in leucocyte subsets and histomorphology in normal-appearing perilesional skin and early and chronic hidradenitis suppurativa lesions. Br J Dermatol 2012; 166 (1): 98-106.
14. Schlapbach C, Hänni T, Yawalkar N, Hunger RE. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. J Am Acad Dermatol 2011; 65 (4): 790-8.

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A RETROSPECTIVE ANALYSIS OF THE PALLIATIVE SURGICAL TREATMENT IN PATIENTS WITH MALIGNANT PLEURAL EFFUSION

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Abstract

Introduction: The formation of malignant pleural effusion (MPE) is a clinical manifestation of an advanced malignancy or its dissemination. The focus of treatment is primarily palliative and aimed at relieving symptoms, especially dyspnoea.

Material and Methods: Clinical data from patients who were hospitalized at the Clinic of Thoracic Surgery, JFMED CU and Martin University Hospital, in the years 2015–2019 were retrospectively explored and statistically analyzed based on their medical records.

Results: From the group of patients with proven MPE (n=67), 32 patients were male (48%) and 35 were female (52%). The mean age was 62.3 years (65.4 for males and 59.4 for females). The three most common primary malignancies were lung cancer (n=24), breast cancer (n=14), and kidney cancer (n=6). In 38 patients with MPE a talc pleurodesis via VATS was performed, with a median survival of 341 days (95% CI 256–859). Drainage following the talc slurry pleurodesis was performed in 10 patients with a median survival of 91.5 days (95% CI 64-NA). Ten patients with MPE underwent drainage only. The overall median survival time after all types of surgical interventions was 301 days (95% CI 207-389 days).

Conclusion: Management of MPE depends on the patient´s prognosis. A definitive intervention is required in patients with a long-term survival, while in patients with a short life expectancy procedures leading to the shortest hospital stay are preferred. Videothoracoscopic procedures with pleurodesis represent an effective treatment for patients with symptomatic MPE with a good performance status, presence of lung re-expansion following pleural drainage or expected survival.

Key words: malignant pleural effusion, videothoracoscopy, pleurodesis, survival

INTRODUCTION

Malignant pleural effusion (MPE) affects a number of patients worldwide and is associated with high morbidity and mortality. It is estimated that it affects more than 100,000 people in Europe [1]. Some authors report that the incidence of pleural cancer with MPE in Europe is estimated to approximately 375,000 to 400,000 patients per year [2]. The survival of patients with MPE is estimated to 3 to 12 months [3]. Although there are no studies documenting the rate of hospitalization of all patients, clinical experience suggests that majority of patients seek medical care primarily for the management of MPE-related symptoms [1].

The most common presenting symptom is breathlessness [3]. As the effusion increases, lung tissue is compressed and atelectasis occurs. Other manifestations include cough,

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fever, pleuritic chest pain, night sweats, and cachexia [4]. The risk of inflammatory complications is significantly higher due to a previous chemotherapy or radiotherapy for a malignant disease [5]. MPEs develop most commonly in patients with lung cancer, followed by breast cancer and lymphoma [2, 6–8]. Less commonly associated malignancies include malignant mesothelioma, gynaecological and gastrointestinal tumours [9]. Approximately 7-11% also occur with unknown primary malignancy [1].

MPEs are confirmed by a detection of malignant population of cells in pleural fluid or in pleural tissue obtained by needle biopsy, thoracoscopy, thoracotomy, or autopsy [6]. Cytological analysis of MPE can provide useful diagnostic information, especially using immunohistochemical methods for differentiating tumour types. However, biopsy remains the gold standard [10, 11]. In many patients with cancer, neoplastic cells cannot be detected in pleural fluid or pleural tissue although the effusion may be caused by cancer. These effusions can be categorized as „paramalignant", in which there is no direct pleural involvement with the tumor and no other cause of the effusion has been identified [12–14]. This can be caused by an obstruction of mediastinal lymph nodes, bronchial obstruction, superior vena cava syndrome [15], or pulmonary embolism [6, 16]. The effusions may be the result of systemic manifestations of cancer or may appear as a result of the therapy, which should be considered [13, 17].

The options of pleural interventions for MPE include thoracentesis, chest tube drainage, insertion of indwelling pleural catheter (IPC), talc pleurodesis via medical thoracoscopy, video-assisted thoracoscopic surgery (VATS) or chest tube (slurry), and thoracotomy [11]. Other methods such as pleurectomy or pleuroperitoneal shunt are rarely used in clinical practice [6, 9, 16, 18]. Persisting or recurrent pleural effusions are usually managed by pleurodesis to improve dyspnoea [19]. This can be performed by VATS with talc poudrage insufflation or by injection of talc slurry into the chest tube [11]. Studies recommend the placement of a tunneled indwelling pleural catheter (IPC) in patients who cannot undergo pleurodesis or have non-expandable lung [19, 20], but in Slovakia IPCs are not yet commonly used. The inserted chest drain can be connected to Heimlich valve, that could be realized if pleural effusion persists and its daily production is high [16]. There have been significant advancements in the management of patients with MPE in the last years, as reflected by the new ERS/EACTS [11] and ATS/STS/STR guidelines [20].

The aim of the presented study is to analyze the clinical data of patients hospitalized at the Clinic of Thoracic Surgery and to evaluate the survival of patients with malignant pleural effusion.

MATERIAL AND METHODS

Patients with fluidothorax, hospitalized at the Clinic of Thoracic Surgery, the Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, and Martin University Hospital from January 2015 to December 2019 were included in the retrospective study. The source of information was a record from their medical documentation. We determined the following parameters of the monitored group: patient´s gender and age, site of primary malignancy, location and character of the effusion. We evaluated procedures performed and median survival times. We also included those patients who were alive at the time of the study.

Talc pleurodesis, as the most common palliative procedure in patients with MPE, is performed at our clinic in two ways – by administering a solution of talc through the chest drain or intrapleural administration of talc poudrage during VATS. When administering talc through the chest drain, the patient must initially undergo a thoracic drainage with evacuation of pleural effusion. When the daily production into the chest drain is below 150 ml, we carry out a controlled chest X-ray and a subsequent talc pleurodesis. We administer talc via a drain using 4g of sterile talc diluted in 50 ml of physiological saline. The chest drain

is clamped for 4 hours and the patient is positioned for at least every half an hour. If the production into the drain is less than 150 ml by the next day, we remove the chest drain. During the administration of talc we give the patient analgesics. There may be transient dyspnoea, pain, fever, or other flu-like symptoms. The second option of talc pleurodesis is its administration through videothoracosopy. In most cases, videothoracoscopy is performed through 2 ports. After evacuation of fluidothorax, possibly, disruption of adhesions or pleural biopsy, we insufflate the talc poudrage from an original sterile bottle. The advantage of this method is the evacuation of fluidothorax with talc plurodesis in one step, the disadvantage is the need for general anesthesia.

The data were explored and analyzed using R Core Team ver. 4.0.2, with the aid of libraries gtsummary, survival, and survminer. The null hypothesis of no difference between two surgical curves was tested by a log-rank test. P-value below 0.05 was used to imply statistical significance. We used the non-parametric Kaplan-Meier method for the survival analysis. The obtained data were correlated with data in published foreign studies. The retrospective study was approved by the Ethics Committee of JFMED CU (protocol No. 75/2019).

RESULTS

The retrospective study included 207 patients who were hospitalized for present fluidothorax. There were created 6 groups. The largest group consisted of malignant pleural effusions (32%), followed by paramalignant effusions (27%) and exudates associated with inflammation (17%). A separate group consisted of „other and not otherwise specified effusions“ (14%; transudates in congestive heart failure, hepar cirrhosis, abscesses, effusions in rheumatoid arthritis, abnormal cytological findings without manifestation of acute inflammation or malignancy). Another group consisted of effusions of non-tumor etiology of hemorrhagic character (6%; most often post-traumatic) and effusions of empyema character (5%).

The group of malignant effusions consisted of effusions in which a primary or secondary pleural tumor was detected by a pleural biopsy or cytology. The diagnosis of pleural carcinosis was supported by a positive videothoracoscopic finding. There were included 67 patients (32 male and 35 female) with an average age of 62.3 years (65.4 for men and 59.4 for women). Thirty-five effusions were right sided (52,2%), 27 were located in the left hemithorax (40,3%), and 5 were bilateral (7,5%). The most frequently diagnosed primary malignancy was lung cancer in 25 patients (37%), followed by breast cancer in 14 patients (21%), kidney cancer in 6 patients (9%), and malignant mesothelioma in 5 patients (7,5%). In 5 patients (7.5%) no primary tumour was identified. Other causes and characteristics of the group are shown in Tab. 1.

The number of patients with paramalignant pleural effusion was 55 (33 men and 22 women). The mean age was 66.2 years (66.6 for men and 65.5 years for women). Lung cancer occurred in 14 patients (25%), breast cancer in 10 patients (18%). Tumors of the gastrointestinal tract accounted for 13% (7 patients), pancreatic cancer for 11% (6 patients), renal cancer for 9,1% (5 patients), gynecological cancer for 5,5% (3 patients), and lymphoma for 7,3% (4 patients). Other concomitant malignancies (prostate cancer, gastrointestinal cancer, liver cancer, myeloma, bladder cancer, unknown origin) were present in one case of each type of these malignancies.

In our study the performed procedures in patients with MPE were evaluated (Fig. 1). VATS procedures were performed in 48 cases (72%), of which 38 cases with macroscopically pleural carcinosis were supplemented by a talc pleurodesis (57%). In 10 patients (15%) VATS and drainage without talc supplementation was performed. Drainage and subsequent talc pleurodesis (talc slurry) were performed in 10 patients (15%) and drainage only in 6 patients (9%). Due to a high daily production into the drain, 16 patients were discharged with the chest tube left on the Heimlich valve and pleurodesis was performed later. Because

Table 1. Primary malignancy, sex, mean age, and median survival in patients with MPE

Malignancy type	Total (n=67)	Male (n=32)	Female (n=35)	Median survival (days)	Mean age (years)
Lung	25 (37%)	12	13	341	65
Breast	14 (21%)	–	14	301	59
Renal	6 (9%)	6	–	131	62
Mesothelioma	5 (7.5%)	3	2	458	66
Gynecological	3 (4.5%)	–	3	26	61
Gastrointestinal	2 (3%)	1	1	328	54
Liver	1 (1.5%)	–	1	151	46
Prostate	1 (1.5%)	1	–	226	79
Thyroid	1 (1.5%)	1	–	219	69
Salivary gland	1 (1.5%)	1	–	256	67
Melanoma	1 (1.5%)	1	–	12	67
Hematologic	1 (1.5%)	1	–	6	65
Prostate	1 (1.5%)	1	–	192	78
Unknown origin	5 (7.5%)	4	1	442	53

of the primary disease and performance status of the patient, therapeutic puncture was performed once with an improvement of the condition. For the ambiguous thoracoscopy with pleural biopsy (suspected mesothelioma), there was indicated a thoracotomy with a confirmation of this diagnosis. A second thoracotomy was performed in a patient with adhesions in the pleural cavity and a tumor of unknown origin in the pulmonary hilum.

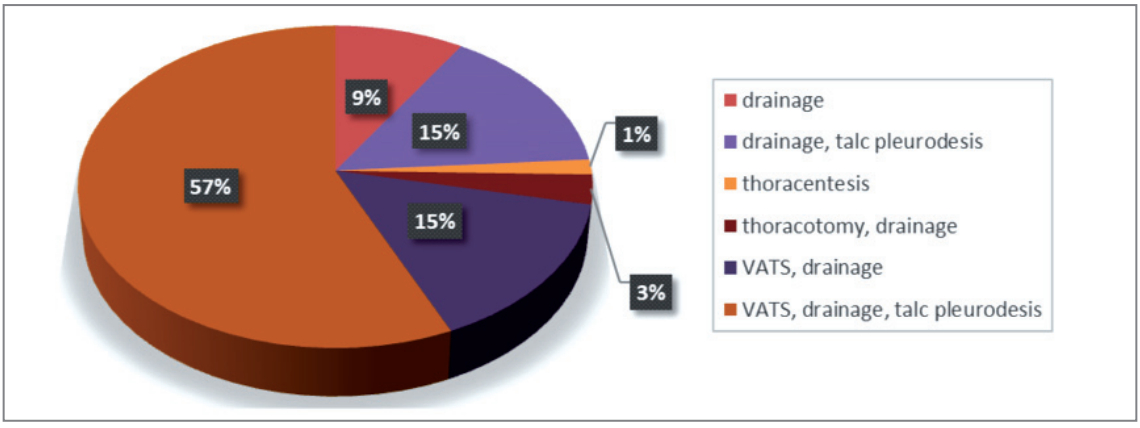

Fig 1. Performed interventions in patients with MPE during hospitalization

We further analyzed the survival of patients with MPE from the date of the intervention. In our study an overall one-year survival from the date of the intervention was achieved by 37% of the patients with MPE (n=25). We recorded 2 deaths during the hospitalization. The median survival time in malignant pleural effusion was 301 days (95% CI 207-389 days). The median survival time was 341 days (95% CI 102-499) for lung cancer patients and 301 days (95% CI 235-NA) for breast cancer patients. Patients with mesothelioma tended to have a longer survival and we recorded worse survival in gynecological-urological malignancies, malignant melanoma, and hematologic malignancy (Tab. 1). Fig. 2 represents the Kaplan-Meier survival analysis with the probability of survival in malignancy type (lung and breast cancer).

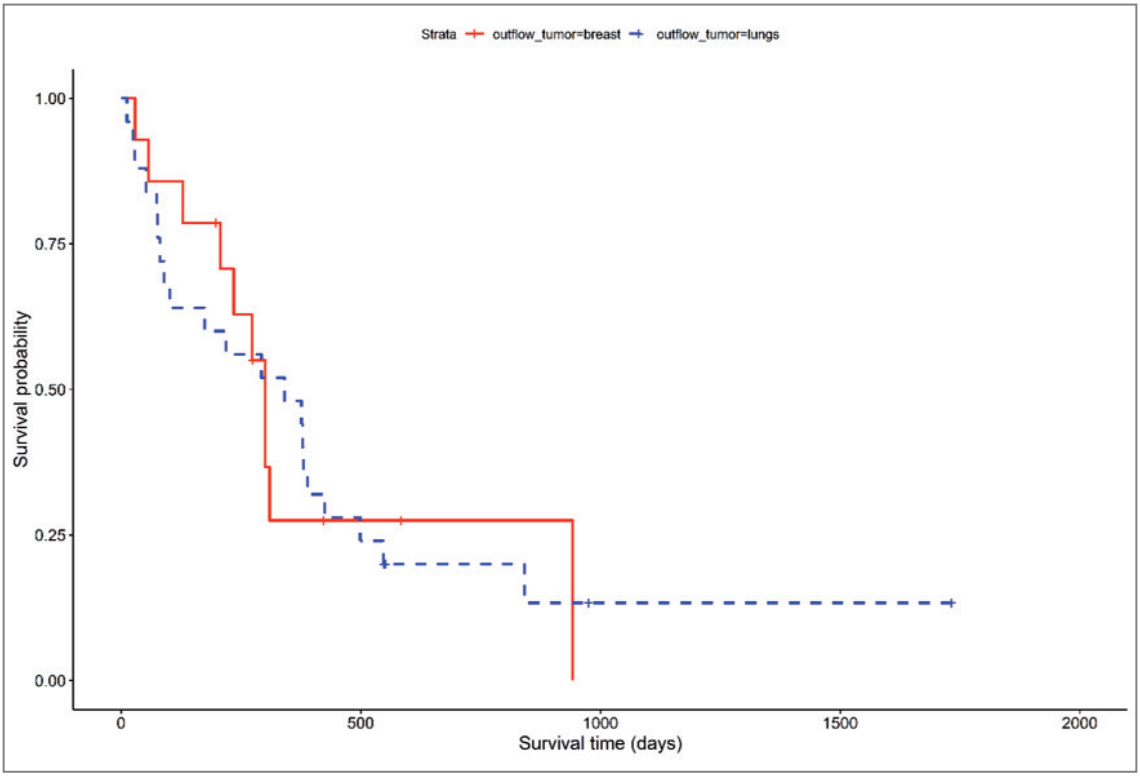

Fig. 2 Kaplan-Meier survival curves for lung and breast cancer

Talc pleurodesis via VATS was performed in 38 patients with a median survival of 341 days (95% CI 256-859 days). Talc slurry pleurodesis was performed in 10 patients with a median survival of 91.5 days (95% CI 64-NA). The survival times appear to be better after VATS pleurodesis, which may be related to the number of interventions performed and also to the fact that patient should have a good performance status and ability to undergo the procedure under general anesthesia. Fig. 3 shows a Kaplan-Meier curves for procedure type and compares probability of survival in two groups.

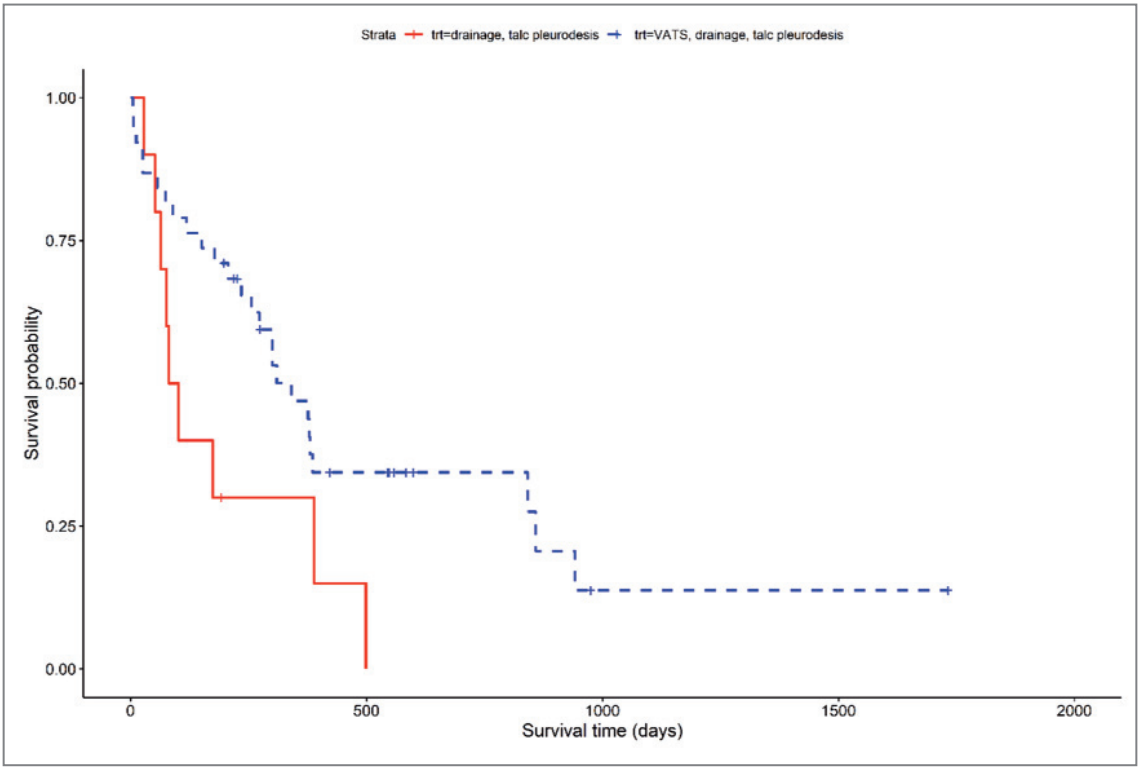

Fig. 3 Kaplan-Meier curves for intervention types

DISCUSSION

In our study MPEs were most commonly caused by a primary lung or breast cancer. Compared with data in the literature reporting malignant lymphoma as the 3rd most common malignity in patients with MPE [2, 6–8], our study had a higher rate of renal carcinoma and malignant mesothelioma (Tab. 1). Paramalignant effusions represent a group in which the propagation of malignant cells in the pleural effusion or pleural histology was not demonstrated. In our group of patients, for example, these were tumors of the gastrointestinal tract and pancreas, in which fluidothorax was present.

The median survival in MPE is ranging from 3–12 months, but can vary significantly according to the performance status of the patient, cell type, staging, and whether a chemosensitive malignancy is present [19]. Some studies report a worse median survival for lung cancer than for breast cancer [9, 21]. In our study the median survival time was 301 days in breast cancer and 341 days in lung cancer patients from the day the intervention was performed (Tab. 1).

Videothoracoscopic procedures with pleurodesis and a median survival of 341 days were the most frequent treatment option of MPE in our study. Foreign studies recommend talc pleurodesis as the treatment of choice for patients with symptomatic MPE. Using long-term indwelling pleural catheters could be an alternative to talc pleurodesis (mostly in patients with trapped lungs or short life expectancy) [20, 22]. The data suggest that thoracoscopic talc poudrage (via VATS or medical thoracoscopy) may be slightly more effective than the slurry for MPE pleurodesis [23]. The treatment depends on factors such as performance status, presence of lung reexpansion following pleural drainage, or expected survival [24].

There are some limitations of this study, as we did not consider the comorbidities of the patient, the treatment of the primary tumour, effusion reccurence, or the prognostic factors. It is stated that the patients receiving first- or second-line systemic treatment have been reported to have a higher risk of MPE recurrence compared to the patients who underwent the treatment of MPE before the systemic treatment [25].

CONCLUSION

The results of our retrospective study show that the choice of the therapeutic approach is adapted to the expected survival of the patient. Procedures leading to the shortest hospital stay and the lowest postoperative morbidity should be reserved for patients with the shortest expected survival. Videothoracoscopic procedure with pleurodesis is the effective treatment for patients with symptomatic MPE with good performance status, presence of lung reexpansion following pleural drainage, or expected survival. The new therapeutic approaches and recommendations have grown but the management of MPE may vary from country to country. Despite advances in therapeutic options, the prognosis remains poor and mortality high. MPEs require sufficient attention and proper management, as they occur in routine clinical practice.

REFERENCES

1. Penz E, Watt KN, Hergott CA, Rahman NM, Psallidas I. Management of malignant pleural effusion: challenges and solutions. Cancer Manag Res. 2017;9:229-241.
2. Ried M, Hofmann HS. The treatment of pleural carcinosis with malignant pleural effusion. Dtsch Arztebl Int. 2013;110(18):313-318.
3. Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ; BTS Pleural Disease Guideline Group. Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. Thorax. 2010;65 Suppl 2:ii32-ii40.
4. Dixit R, Agarwal KC, Gokhroo A, et al. Diagnosis and management options in malignant pleural effusions. Lung India. 2017;34(2):160-166.
5. Habal P, Omran N, Jankovičová K, Kodělková K, Krejsek J, Manďák J. Torakoskopicky navozená chemická pleurodéza v léčbě maligního pleurálního výpotku. Onkologie. 2014;8(1):35-8.
6. Sahn SA, Huggins JT. Malignant pleural effusions. In: Grippi MA, editors. Fishman's pulmonary diseases and disorders. 5th ed. NewYork: McGraw Hill Education;2015. p. 1164-1187.
7. Jany B, Welte T. Pleural Effusion in Adults-Etiology, Diagnosis, and Treatment. Dtsch Arztebl Int. 2019;116(21):377-386.
8. Meriggi F. Malignant Pleural Effusion: Still a Long Way to Go. Rev Recent Clin Trials. 2019;14(1):24-30.
9. Skok K, Hladnik G, Grm A, Crnjac A. Malignant Pleural Effusion and Its Current Management: A Review. Medicina (Kaunas). 2019;55(8):490.
10. Huťka Z. Karcinóm pľúc z pohľadu cytopatologickej diagnostiky. In: Kavcová E, Halašová E, Dzian A, editors. Karcinóm pľúc. UK Bratislava, JLF Martin; 2010. p. 216-224.
11. Bibby AC, Dorn P, Psallidas I, Porcel JM, Janssen J, Froudarakis M et al. ERS/EACTS statement on the management of malignawnt pleural effusions. Eur J Cardiothorac Surg. 2019;55:116-32.
12. Sahn SA. Pleural diseases related to metastatic malignancies. Eur Respir J. 1997;10(8):1907-1913.
13. American Thoracic Society. Management of malignant pleural effusions. Am J Respir Crit Care Med. 2000;162(5):1987-2001.
14. Villanueva AG. Management of Malignant Pleural Effusions. Principles and Practice of Interventional Pulmonology. 2012;665-674.
15. Rice TW, Rodriguez RM, Barnette R, Light RW. Prevalence and characteristics of pleural effusions in superior vena cava syndrome. Respirology. 2006;11(3):299-305.

16. Plutinský J. Karcinóm pľúc a postihnutie pleury. In: Kavcová E, Halašová E, Dzian A, editors. Karcinóm pľúc. UK Bratislava, JLF Martin; 2010. p. 263–293.
17. Heffner JE. Diagnosis and management of malignant pleural effusions. Respirology. 2008;13(1):5-20.
18. Ludwig C, Stoelben E. Chirurgische Therapie des malignen Pleuraergusses. Zentralblatt für Chirurgie. 2008;133(3):218-221.
19. Koegelenberg CFN, Shaw JA, Irusen EM, Lee YCG. Contemporary best practice in the management of malignant pleural effusion. Ther Adv Respir Dis. 2018;12.
20. Feller-Kopman D, David J. Management of Malignant Pleural Effusions. An Official ATS/STS/STR Clinical Practise Guideline. American Journal of Respiratory and Critical Care Medicine. 2018; 198(7):839-349.
21. Bell D, Wright G. A retrospective review of the palliative surgical management of malignant pleural effusions. BMJ Support Palliat Care. 2014;4(2):161-166.
22. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up [published correction appears in Ann Oncol. 2019 May;30(5):863-870]. Ann Oncol. 2018;29(Suppl 4):iv192-iv237.
23. Bhatnagar R, Laskawiec-Szkonter M, Piotrowska HEG, et al. Evaluating the efficacy of thoracoscopy and talc poudrage versus pleurodesis using talc slurry (TAPPS trial): protocol of an open-label randomised controlled trial. BMJ Open. 2014;4:e007045.
24. Clive AO, Kahan BC, Hooper CE, et al. Predicting survival in malignant pleural effusion: development and validation of the LENT prognostic score. Thorax. 2014;69(12):1098-1104.
25. Abrão FC, de Abreu IRLB, de Oliveira MC, et al. Prognostic factors of recurrence of malignant pleural effusion: what is the role of neoplasia progression? J Thorac Dis. 2020;12(3):813-822.

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ECSTASY-INDUCED MALIGNANT HYPERTHERMIA WITH FATAL OUTCOME: A CASE REPORT

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Abstract

3,4-methylenedioxymetamphetamine (MDMA), also known as “ecstasy”, “tulips”, or “Molly”, is an increasingly used "recreational drug" particularly among teenagers and young adults along with the widespread conviction that MDMA is a “safe drug". The reason for this substance being abused is a desire for closeness to other people, develop a greater tolerance of their views and feelings, and even to touch them physically. According to these effects MDMA is classified also as an “*empatogenic*” or “*entactogenic*”. Although MDMA is used for the above-mentioned socially acceptable purposes, in many individuals the drug usage is followed with side-effects varying from mild to severe, potentially even life-threatening. One of the most significant complication of MDMA intoxication is hyperthermia in the consumer. Authors presented a case of MDMA toxicity with severe hyperthermia (42 ºC) with a fatal outcome to the ecstasy-influenced subject. The aim of this article is to describe the effects of ecstasy, the "recreational drug" widely used in local pubs, dance clubs, and during open air festivals, even in the Slovak Republic.

Keywords: 3,4-methylenedioxymethamphetamine, MDMA, ecstasy, hyperthermia, drug toxicity

INTRODUCTION

3,4-methylenedioxymethamphetamine (MDMA), commonly known as “ecstasy”, is a ring-substituted amphetamine derivative with stimulant and hallucinogenic properties, used as a popular "recreational drug" (1, 2). Effects, for which such a psychoactive substance is usually used by young people, are experiences of a relaxed, euphoric state characterized by increased empathy, openness, communication, and tranquility (2). MDMA as a "dance drug" is linked with attendance at “raves”, all-night dance events with fast-paced electronic music (2). Mood-enhancing properties of this psychoactive substance could be summarized in the 3 Es: energy, empathy, and euphoria (3). Although MDMA is often considered as being a “safe” drug, use of this stimulant is associated with significant morbidity and mortality (3, 4). Typical "recreational" doses of MDMA are 1 to 2 mg/kg. The onset of effects occurs between 30 and 60 minutes after ingestion (2). The side-effects of ecstasy vary from mild to severe, potentially life-threatening. Mild clinical symptoms and signs seen with MDMA are tachycardia, mydriasis, feeling of dry mouth, profound sweating, and *bruxism* (jaw clenching) (3). Severe adverse reaction as hyperthermia, seizures, hypertensive crises, cardiac dysrhythmias, metabolic disturbances, disseminated intravascular coagulation (DIC), rhabdomyolysis, acute kidney or liver failure, cerebrovascular episodes, psychiatric disturbances, or accidents/injuries can lead to fatalities related to MDMA intoxication (3, 4, 5). The authors report a case of a young man who consumed MDMA and within a short time developed hyperthermia, delirious behavior, and seizures leading to death. The aim of this article is to point out the side-effects of such an “innocent" drug, popular even in Slovakia.

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CASE REPORT

A 23-year-old previously healthy male was admitted to the emergency department after a sudden onset of generalized seizures at a local rave party. The consuming of any illicit drugs by the subject was denied by his friends. There was seriously pronounced verbal and brachial aggression, agitation, and seizures escalated into the patient´s consciousness disorders (Glasgow coma scale of 8) prior to the hospital admission. Initial vital signs revealed an oral temperature of 42ºC, a heart rate of 130 beats per minute with a blood pressure drop to 100/70 mm Hg. Initial blood glucose was 4.2 mmol/l. Physical examination showed hot sweaty skin with diffuse intermittent myoclonic activity and mydriasis with massive conjunctival hyperaemia. After arrival to the hospital the patient´s condition dramatically worsened, accompanied by profuse vomiting, sudden quantitative decrease of consciousness (Glasgow coma scale of 3), and cessation of vital functions. The skin of the victim was mottled with marked cyanosis on the upper part of the body. The patient underwent forceful resuscitation involving endotracheal intubation, after 45 minutes of resuscitation efforts the patient was declared dead. Urine toxicology screening for drugs of abuse was not performed by paramedics or ambulance before his death. The cause of death in the presented case was hyperthermia by lethal MDMA intoxication.

Autopsy

The external examination revealed upper body part cyanosis with demarked multiple petechial haemorrhages localised mainly on the victim's torso. The internal examination revealed gross congestion and oedema of all internal organs (brain 1,620 g, right lung 1,020 g, left lung 730 g). All other macroscopical findings were in accordance with the patient´s age as well as histopathological findings which were non-specific (interstitial myocardial oedema, massive pulmonary oedema, brain oedema).

Toxicology

Post-mortem forensic toxicology revealed elevated serum concentrations of 3,4-methylenedioxymethamphetamine (MDMA) (437 ng/ml) and 3,4-methylenedioxyamphetamine (MDA) (398 ng/ml). Urine toxicology screen for psychoactive substances was positive for amphetamine (AMP), methamphetamine (MET), and 3,4-methylenedioxymetamphetamine (MDMA).

DISCUSSION

3,4-methylenedioxymethamphetamine (MDMA) is a ring-substituted derivative of methamphetamine (**Fig. 1**). It was first synthetized in 1914 and later, in the 1970s, was evaluated as an adjuvant treatment to the psychotherapy. MDMA was becoming widely available recreationally since then. Therefore, in 1985 the drug was placed by U.S. Drug Enforcement Administration on Schedule I of controlled substances (6).

MDMA is usually taken orally in the form of tablets or pills. Less frequently, it can also be administered intravenously or by "snorting" the powder. Ecstasy is sold commonly as tablets of various colours weighing 50–150 mg, stamped with a wide variety of symbols. The chemical composition of tablets varies based on MDMA content. Many ecstasy tablets contain psychoactive substances other than MDMA such as dextromethorphan, amphetamine, methamphetamine, ketamine, or caffeine. Thus, a drug sold as "ecstasy" may be MDMA but also MDEA (methylenedioxyethylamphetamine), MDA (methylenedioxyamphetamine), MPA (para-methoxyamphetamine), MBDB (3,4-methylenedioxy-phenyl-N-methylbutanamine), ephedrine, or mixtures of these as showed by analysis of several different laboratories. Tablets containing 60–80 mg of MDMA are considered as a high-quality substance (5, 6).

Desired effects after ingestion of typical "recreational" dose of MDMA (50–150 mg) appear within 30 to 60 minutes and last for 4 to 6 hours. A peak plasma concentration of MDMA

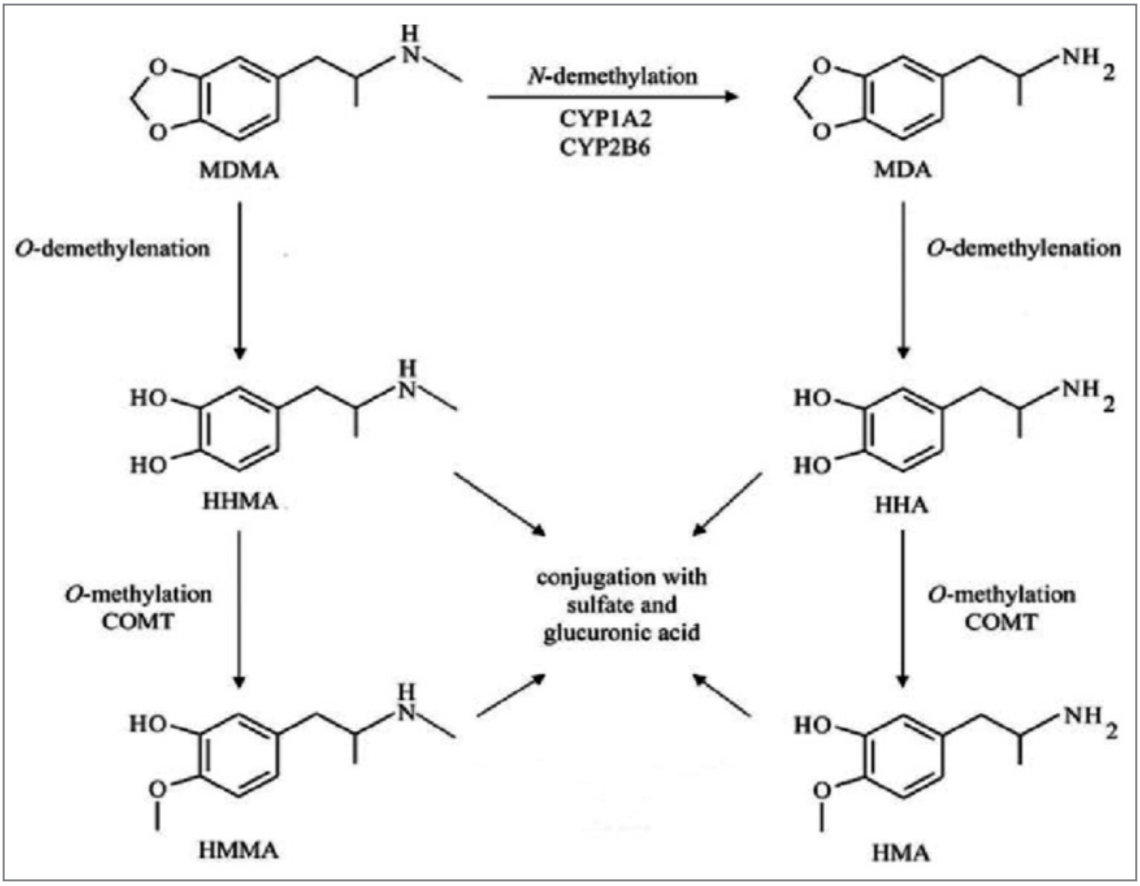

Fig. 1 The metabolism of MDMA (6).

is reached approximately 2 hours after the oral administration (2, 6). The plasma half-life of MDMA is about 8 to 9 hours. MDMA and its first metabolite, MDA (methylenedioxyamphetamine), are pharmacologically active but the hydroxylated metabolites probably do not significantly contribute to the overall effects of the drug (5). MDMA causes the release of the monoamine neurotransmitters (serotonine, noradrenaline, dopamine) in the central nervous system. Anyway, MDMA acts also by binding to and inhibit their reuptake inhibitors at the synapse, principally serotonin. The result is an acute increase in the intra-synaptic concentration of these neurotransmitters, followed by a rather lengthy period of depletion. The mentioned compounds are involved in the control of mood, sleep, autonomous nervous system, as well as in the central control of thermoregulation (7, 8). MDMA effects lead to the activation of mechanisms that conserve and generate the heat and serotonin syndrome is probably the most extreme of these effects (3). Increase of cortisol, prolactin, and adrenocorticotropic hormone blood levels has been shown after MDMA administration and it has been suggested that prolactin may be responsible for the emotional closeness feeling, simulating post-orgasmic state (9).

Physical effects as endurance, sense of energy, sexual arousal, and wakefulness are accompanied by psychological effects described as a sense of euphoria, well-being, sharpened sensory perception, greater sociability, and close feelings to other people (*entactogenicity* of MDMA). In summary, the desired effects for which the drug is used are similar to other amphetamines (e.g. methamphetamine) and hallucinogens (LSD) (5, 6).

Side-effects of MDMA vary from mild symptoms (tachycardia, trismus, bruxism) to those that are rare but potentially life-threatening. These are not clearly dose-dependent but could be interpreted as idiosyncratic (2). Hence, even a small increase in dosage may carry a risk of serious toxicity. The most important MDMA-induced life-threatening reaction is hyperthermia that can lead to rhabdomyolysis, DIC, and acute renal failure. The increased muscle activity (seizures, jerky spasms of the whole body) for dozens of minutes, together with a direct action of the drug on the thermoregulatory system, result in an extensive increase of body temperature, whereas high ambient temperature, exertion (e.g. prolonged high-energy dancing before an attack of hyperthermia), and dehydration may act as additional permissive factors. Thus, most of the severe morbidity and mortality associated with MDMA use can be attributed to hyperthermia effects (2). Although the side-effect of MDMA consumption could be hypertension, on the other side hyperthermia could lead to vasodilatation result in hypotension except from the fact high body temperature cause permanent damage of brain regulation centers. One hypothesis of the user´s susceptibility for hyperthermia suggests possible defective metabolism of the drug in organism (4, 5, 10). The process of biotransformation of MDMA takes part mainly in the liver, largely by the hepatic cytochrome-P450 isoform CYP2D6. Some of different enzymes involved in the degradation of MDMA appear to be saturated at relatively low drug concentrations. Hence, when these enzymes are saturated and MDMA dose is increased, disproportional enhancement in blood and brain concentrations of the drug occur. As 5–9 % of Caucasians displays genetic polymorphisms of CYP2D6, this part of population is being suspected to be at a higher risk of acute MDMA toxicity. Unfortunately, the genetic testing of patients intoxicated by ecstasy has not been carried out (2, 3, 11). Another possible cause of toxicity of MDMA are ecstasy pill contaminants, so negative drug screen for any additional substances must be interpreted cautiously. There may be present co-ingestants that are not typically detectable (e.g. lysergic acid diethylamide, LSD) or may not be tested for (e.g. cocaine, ketamine) (11).

In the presented case the toxicology examination revealed the serum concentration of MDMA (437 ng/ml) significantly higher than the usual "recreational" dose (100-150 ng/ml). Lethal serum concentration ranges between 500 ng/ml-10,000ng/ml, but many authors point out the degree of the seriousness depends likewise on factors other than the drug concentration itself (2, 5, 6). The higher concentration of the first metabolite MDA (398 ng/ml) declared a prolonged metabolic degradation of the drug in the body. The delayed desirable drug effects (about 1–2 hours) may lead to a repeated use of MDMA, which means a consequently increased dosage before the onset of the desired effects, which may appear already in the level of intoxication. According to the testimony of the friends of the deceased there was a suspicion of adding a foreign substance into his beverage by an unknown person, which should be legally considered as a criminal act. The physical properties of ecstasy allow only a partial dissolution of the powder form of MDMA in water together with a significant change in the taste of the beverage. Thus, an involuntary consumption of ecstasy dissolved in any kind of beverage seems very unlikely.

The presented case of fatal outcome of ecstasy overdose in a young man presented by the authors points to a rare but severe MDMA-induced toxicity, in contrary with the mistaken belief in the safe use of MDMA. The dangerous trend of ecstasy (MDMA) consumption as a “recreational drug” is widely accepted among young adults and teenagers, even in the Slovak Republic. According the Annual Report of National Criminal Agency (NAKA) of the Ministry of Inferior of the Slovak Republic, there were 2,370 pills of ecstasy seized in Slovakia by the police authorities in 2017 (12). However, high this number seems to be, it represents only a "peak of an iceberg" of the Slovak drug scene. Emergency doctors and physicians should be alert to the existence of ecstasy drug in the Slovak Republic, realize the growing tendency of using that drug within the youngsters at specific occasions, and recognize its extremely dangerous side-effects threatening health or life of otherwise healthy population of young people.

REFERENCES

1. Meyer JS. 3,4-methylenedioxymethamphetamine (MDMA): current perspectives. Subst Abuse Rehabil 2013; 4: 83-89.
2. Armenian P et al. Multiple MDMA (Ecstasy) overdoses at a rave event: a case series. J Intensive Care Med 2012; 28 (4): 252-258.
3. Hall AP, Henry JA. Acute toxic effects of "Ecstasy" (MDMA) and related compounds: overview of pathophysiology and clinical management. Br J Anaesth 2006; 96 (6): 678-685.
4. Connolly E, O´Callaghan G. MDMA toxicity presenting with severe hyperpyrexia: a case report. Crit Care Resusc 1999; 1: 368-370.
5. Kalant H. The pharmacology and toxicology of "ecstasy" (MDMA) and related drugs. CMAJ 2001; 165 (7): 917-928.
6. Baselt, RC. Disposition of toxic drugs and chemicals in man. Tenth Edition. California: Biomedical Publications; 2014.
7. Fiege M etal. Induction of malignant hyperthermia in susceptible swine by 3,4- Methylenedioxymethamphetamine ("Ecstasy"). Anesthesiology 2003; 99 (5):1132-1136.
8. Green AR et al. The pharmacology and clinical pharmacology of 3,4-methyledioxymethamphetamine (MDMA, "Ecstasy"). Pharmacol Rev 2003; 55: 463-508.
9. Passie T et al. Ecstasy (MDMA) mimics the post-orgasmic state:impairment of sexual drive and function during acute MDMA-effects may be due to increased prolactin secretion. Med Hypotheses 2005; 64: 899-903.
10. Lang et al. Fatal Ecstasy-induced malignant hyperthermia with rhabdomyolysis. A case report. Rom J Leg Med 2016; 24: 212-215.
11. Manish et al. Methylenedioxymethamphetamine (ecstasy)-related hyperthermia. J Emerg Med 2005; 29 (4): 451-454.
12. Národná kriminálna agentúra (NAKA), Národná protidrogová jednotka, Prezídium Policajného zboru SR, Ministerstvo vnútra SR. Správa o stave a vývoji drogovej scény na území Slovenskej republiky v roku 2017. Bratislava; 2018.

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SPINDLE CELL MELANOMA HARBORING A NODULE OF EPITHELOID CELL MELANOMA COMPONENT: A STUDY OF A DIAGNOSTICALLY CHALLENGING CASE

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Abstract

Background: Melanoma is a very heterogeneous human neoplasm. In addition to four major (conventional) histologic subtypes a number of uncommon variants do exist.

Objective: An unusual case of a spindle cell melanoma (SCM) containing a demarcated nodule of conventional epitheliod cell melanoma component is described.

Material and Methods: A 71-year-old man manifested with a protuberated ulcerated skin tumor arising on the right forearm. The resected biopsy was analyzed immunohistochemically with a variety of anti-human antibodies.

Results: The tumor consisted of a highly cellular mass of spindle-shaped cells without any significant intratumoral fibrosis. In addition, a nodule of epithelioid cell tumor component was present within the lesion. The spindle cell component showed a disperse reactivity for S100 protein and was negative for other melanocytic markers. It exhibited a very high mitotic activity and proliferation Ki-67 index. No melanin pigment was detected. In contrast, the epithelioid cell component was strongly positive for S100 protein, Melan-A/MART-1, HMB-45, and PNL-2. The mitotic and proliferation indices were much less pronounced and melanin deposits were visible. A diagnosis of a non-desmoplastic SCM harboring a nodule of epithelioid cell melanoma component was established.

Conclusion: SCM often posses a diagnostic dilemma because its histomorphology is atypical and its immunohistochemical profile may differ from other subtypes of melanomas. The present paper points out this uncommon histopathological entity that may sometimes be encountered in dermatopathological practice and that requires more complex diagnostic approach.

Keywords: malignant melanoma, spindle cell component, epithelioid cell component, S100 protein

INTRODUCTION

Melanoma is one of the most aggressive malignancies in humans with a high mortality rate (1–3). Although it accounts for only 5% of all skin cancers, it is responsible for more than 77% of skin cancer-related deaths (2). This prognostically unfavorable phenomenon is exacerbated by the fact that the tumor has shown a rapid increase in incidence over the last few decades (2, 4). There are four major (conventional) histologic subtypes of cutaneous melanoma: superficial spreading melanoma, nodular melanoma, lentigo maligna/lentigo maligna melanoma, and acral lentiginous melanoma (1, 5). Although this classification has been accepted by many over the years, its artificiality and limitations have clearly been documented (5). In fact, melanoma is one of the most heterogeneous and complex human neoplasms (5). Consequently, on a regular basis one encounters melanomas that are difficult to categorize as one of the four major subtypes (5). A number of uncommon and unusual histologic variants have been described until now (Table 1) (5–7). Separating them from conventional subtypes mainly serves to remind pathologists of the morphologic diver-

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sity of melanomas and to point out diagnostic pitfalls (6). The recognition and delineation of both conventional and less common variants of melanoma correspond to a wide range of clinical, microscopic, genetic, and molecular phenotypic characteristics (5).

Table 1 Classification scheme of histological subtypes and variants of malignant melanoma. (5–7)

A. Major (conventional) histologic subtypes	
1. superficial spreading melanoma	
2. nodular nelanoma	
3. lentigo maligna/lentigo maligna melanoma	
4. acral lentiginous melanoma	
B. Uncommon histological subtypes and variants	
spindle cell melanoma	metaplastic melanoma
desmoplastic melanoma	baloon cell melanoma
neurotropic melanoma	signet-ring cell melanoma
nevoid melanoma	myxoid melanoma
minimal-deviation melanoma	small cell melanoma
equine/animal-type melanoma	rhabdoid melanoma
malignant blue nevus	angiotropic melanoma

Melanomas with predominant spindle cell morphology comprises a spectrum of tumors. If associated with a marked fibrous stroma throughout the invasive component, they are designated desmoplastic melanoma (6). If intraneural and/or perineural invasion is prominent and a neuroma-like growth pattern is present, the term neurotropic melanoma may be applied (6). If the tumor does not have any of these features, it is called spindle cell melanoma (SCM), not otherwise specified (or non-desmoplastic SCM) (6). The main diagnostic problem related to melanomas with predominant spindle cells is their potential confusion with various types of sarcoma or sarcomatoid carcinoma (6). In this journal an interesting case of a desmoplastic melanoma has been recently published by Adamicova et al. (8). Herein, another unusual case of a non-desmoplastic SCM containing a demarcated nodule of conventional epitheliod cell melanoma component is described.

CLINICAL SYNOPSIS

A 71-year-old man manifested with a painless slow-growing tumor of the skin arising on the right forearm. On physical examination it appeared as a well-defined protuberated light-brownish tumor mass. A presumptive clinical diagnosis was a hemangioma. A total surgical extirpation of the lesion was carried out at the Surgical Outpatient Department.

MATERIAL AND METHODS

The formalin-fixed resected biopsy consisted of the skin and subcutis (25 x 20 mm) with a prominent dome-shaped ulcerated tumor measuring 17 x 14 mm. The specimen was processed into six paraffin-embedded tissue blocks which were stained with hematoxylin-eosin (H&E). Selected sections were then analyzed immunohistochemically with a variety of anti-human antibodies (see below).

PATHOLOGY RESULTS

Histology revealed a protuberated tumor with an extensive ulceration and a necrotic detritus at the base of the ulcer. It consisted of a highly cellular mass of atypical, gently eosinophilic spindle-shaped cells in a fascicular growth pattern without any significant intratumoral fibrosis (Figure 1). They showed vesicular cigar-shaped nuclei and numerous mitotic figures. In addition, a circumscribed nodule of epithelioid cell tumor component was visible within the lesion (Figure 2). This cell population had abundant, slightly basophilic cytoplasm with large round nuclei and prominent nucleoli and contained much less mitotic figures. At first glance, the two components were histologically clearly different, albeit both were undoubtedly malignant. A further analysis confirmed not only distinct histomorphology but also differences in the immunophenotype, mitotic and proliferation rates, and a presence of melanin. They are described in detail in the Table 2. Briefly, the spindle cell component, which comprised the vast majority of tumor tissue, showed a disperse reactivity for S100 protein (Figure 3) and was negative for other melanocytic markers, i.e. Melan-A/MART-1 (Figure 4), HMB-45 (Figure 5) and PNL-2. It exhibited a very high mitotic activity and proliferation Ki-67 index (Figure 6). No melanin pigment was detected (Fontana-Masson staining). In contrast, the epithelioid cell component was strongly positive for S100 protein, Melan-A/MART-1, HMB-45, and PNL-2. The mitotic and proliferation indices were much less pronounced and melanin deposits were visible. Both tumor parts were positive for vimentin and negative for polyclonal cytokeratins (AE1/AE3), high molecular weight cytokeratins (HMWCK), CK5/6, p63, desmin, α-smooth muscle actin, and CD34. In the contex of overall histopathology and immunoprofile, a final diagnosis of a non-desmoplastic SCM harboring a nodule of conventional epithelioid cell melanoma component was established. Other prognostic parameters (not listed in the Table 2) were as follows: Breslow index 6.9 mm, vertical growth phase, Clark's level V, tumor-infiltrating lymphocytes and regression absent, lymfovascular invasion absent, perineural spreading present, and tumor microsatellite present. DNA isolated from the formalin-fixed and paraffin-embedded tissue (FFPE) material using Cobas® DNA Sample Preparation Kit was tested for the presence of the most common somatic mutations V600E, V600D, V600E2, and V600K of the BRAF gene. DNA was isolated from both histological components of the tumor separately. The testing was carried out at cobas® Z480 platform (Roche Molecular Systems, Inc., CA, USA) using CE-IVD cobas® 4800 BRAF V600 Mutation Test Kit (Roche Molecular Systems, Inc., CA, USA) following the manufacturer´s instructions. These mutations can be detected with

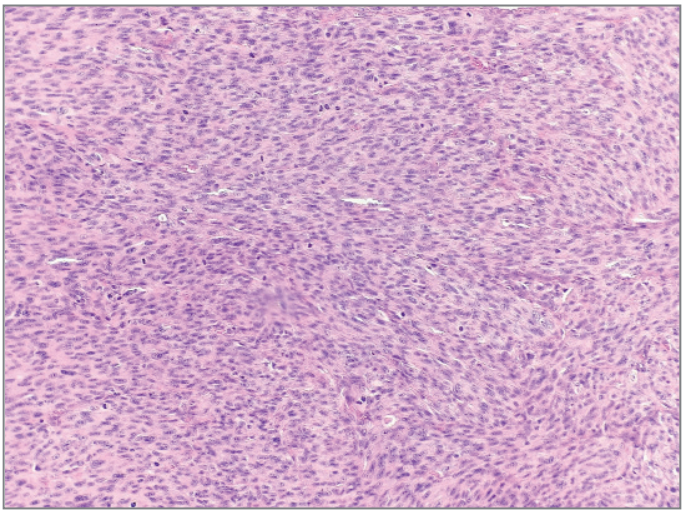

Fig. 1 Highly cellular mass of mitotically active spindle-shaped neoplastic cells. (H&E, magnification 40x)

a sensitivity of ≥ 5% mutant sequences in the background of wild-type DNA. The evaluation of the presence of the mutation was automatic using cobas® 4800 version 2.1 software following the manufacturer´s instructions. A molecular testing for BRAF gene mutations showed negative results in both tumor components.

After sending the final result of the pathologist's report, the authors have not had any information about further clinical management of the patient, but this matter was not a goal of this paper.

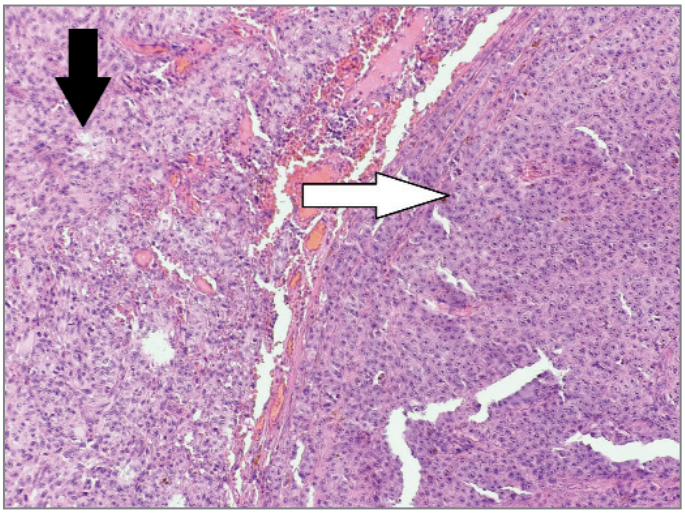

Fig. 2 Interface between a spindle cell component (left black arrow) and a nodule composed of epithelioid cell population (right white arrow). (H&E, magnification 40x)

Table 2 Summary of selected findings in both tumor components. (mf/1mm^2 – number of mitotic figures per 1mm^2, * both typical and atypical mitoses were calculated)

Parameter	Spindle cell component	Epithelioid cell component
proportion of tumor mass	90 %	10 %
mitotic rate	> 25 mf*/1mm^2	7 mf*/1mm^2
Ki-67 index	90 %	25 %
ulceration	present	absent
melanin pigment	absent	present
necrosis	absent	absent
S100 protein	disperse expression	diffuse expression
melan-A, HMB-45, PNL-2	negative	diffuse expression
BRAF mutation	negative	negative

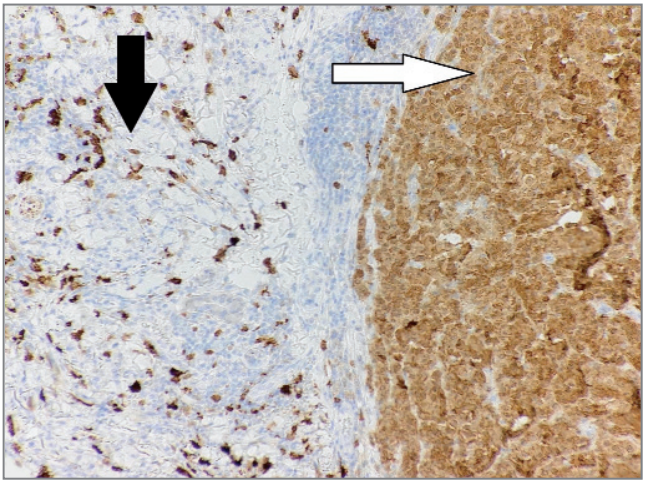

Fig. 3 S100 protein expression. Diffuse strong positivity in epithelioid cell component (right white arrow) and disperse positivity in spindle cell component (left black arrow). (magnification 40x)

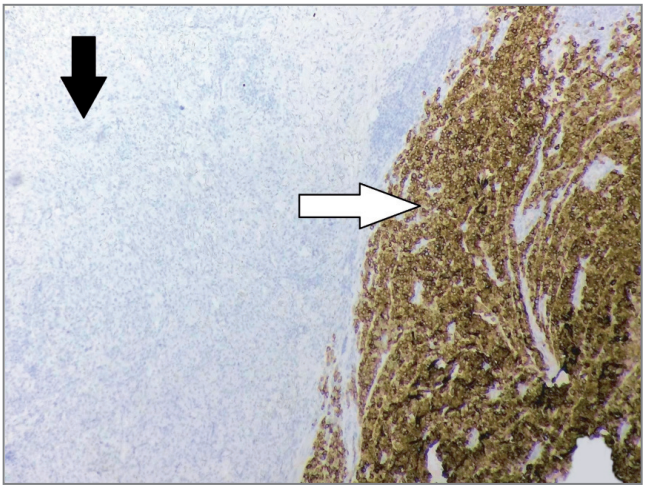

Fig. 4 Melan-A/MART-1 expression. Diffuse strong positivity in epithelioid cell component (right white arrow), while spindle cell component is completely negative (left black arrow). (magnification 20x)

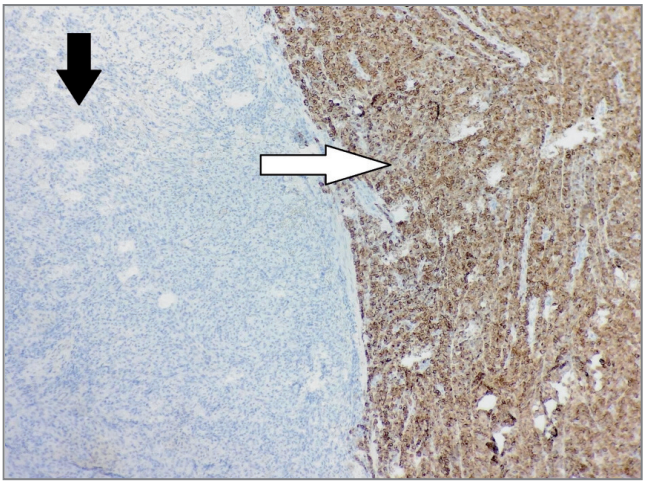

Fig. 5 HMB-45 expression. Diffuse strong positivity in epithelioid cell component (right white arrow), while spindle cell component is completely negative (left black arrow). (magnification 20x)

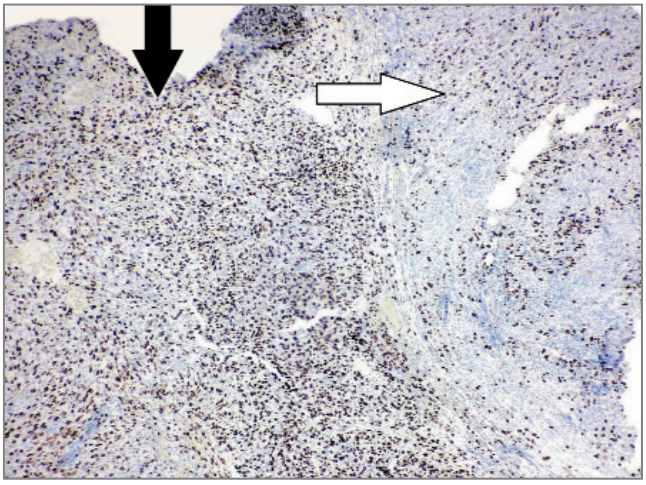

Fig. 6 Ki-67 antigen expression. Proliferation index is much more pronounced in spindle cell component (left black arrow) than in epithelioid cell component (right white arrow). (magnification 20x)

DISCUSSION

Spindle cell melanoma is an uncommon histologic variant of malignant melanoma composed of spindled neoplastic melanocytes arranged in sheets and fascicles (6,9,10). In routine biopsy practice this term serves as an umbrella term for non-desmoplastic spindle cell and desmoplastic melanoma category. Its incidence has been variably reported between 3–14% of all melanoma cases (including desmoplastic melanoma) (9). However, an accurate occurrence is difficult to estimate. In a study of Minarikova et al. (4) no SCM variant has been mentioned among 112 new cases of malignant melanoma registered at the Skin Cancer Department at the Martin University Hospital in year 2017. The results may depend on the age distribution, sex, and ethnicity of the given study cohort. Non-desmoplastic SCM occurs more frequently in men with a median age of 66–68 years (9,10), agreeing with our observation. In contrast to desmoplastic melanoma, which arises more frequently on the head and neck region (1,8,10), non-desmoplastic SCM can occur essentially anywhere on the body, most often on the trunk (10). The diagnosing of SCM is usually challenging and awareness of its clinical and histopathological features as well as immunohistochemical markers are essential to reach the correct diagnosis (9). As a distinct nosologic entity, the SCM brings several diagnostic pitfalls. First, since it usually lacks melanin pigment it grossly mimics other amelanotic lesions (6,9). In fact, amelanotic melanomas are great masqueraders that can mimic a range of skin pathologies including inflammatory lesions and also benign tumors such as hemangioma, pyogenic granuloma, lichen planus-like keratosis, or intradermal nevus that are not routinely excised (11). That is probably why the present case was also clinically considered a benign tumor, i.e. hemangioma. Second, the histopathologic features of SCM are often confused with those of other mesenchymal or epithelial neoplasms (9). Therefore, because of their atypical histomorphology, spindle cell and desmoplastic melanomas may reveal their identity as melanoma only after a first set of adjunct tests, typically including immunophenotyping (10). Third, although an immunohistochemistry is a crucial tool in distinguishing SCM from other malignancies, the SCM may show an unusual immunophenotype and even be negative for classic melanocytic markers (10). Those that are more specific for conventional melanoma generally show poor sensitivity for SCM lesions. American investigators (12) reviewed a series of papers that studied markers for their capacity to detect spindle cell and desmoplastic melanomas. Among them, the S100 protein showed a sensitivity of 98.7%, but the rates of positive staining for Melan-A/MART-1 and HMB-45 were only 21.6% and 17.6%, respectively (12). Newer antibody PNL-2 have not

yielded more promising results. In a study of Busam et al. (13) only 1 of 13 desmoplastic melanomas (7.7%) reacted with PNL-2. In this regard, the S100 protein is by far the most reliable marker. The present case is excelent for demonstrating the different immunophenotypes of two distinct melanoma variants within a single lesion. Such cases are quite uncommon in dermatopathologic practice. Particularly the presence of a conventional nodular epithelioid melanoma component exhibiting a typical positivity for all melanocytic markers was very helpful for establishing the final diagnosis. The coexistence of two histologic variants of melanoma within a single lesion is a consequence of intratumor phenotypic heterogeneity. It has been well documented (1, 14, 15) that the mutation rate of melanoma is very high and it strikingly increases with tumor progression. A high number of clones harboring various mutations contribute to an exceptional level of intratumor diversity in melanoma. Even metastases may originate from different subclones of the primary lesion (14). In our case there were undoubtedly at least two different neoplastic cell clones. Further research addressing this issue is very perspective since levels of tumor heterogeneity in advanced-stage melanomas hinder accurate diagnosis and effective treatment and adversely affect a personalized cancer medicine strategy. Currently, the only biomarker that predicts a therapeutic response to so called target therapy in advanced melanoma is a BRAF gene mutation status (15). Targeted therapy with BRAF inhibitors is associated with significant long-term treatment benefit in patients with BRAF-mutated melanoma (15). Therefore, molecular testing for BRAF mutations is a priority in determining the course of therapy. Although the BRAF V600 mutations have been detected only in 31% of spindle cell and 5% of desmoplastic melanomas (10), given the treatment implications, it argues for standard BRAF testing even in such uncommon melanoma subtypes.

CONCLUSION

Spindle cell melanoma often posses a diagnostic dilemma because its histomorphology is atypical and its immunohistochemical profile may differ from other subtypes of melanomas. The present paper points out this uncommon histopathological entity that may sometimes be encountered in dermatopathological practice and that requires more complex diagnostic approach.

REFERENCES

1. Elder DE, Massi D, Scolyer RA, Willemze R. WHO Clasification of Skin Tumours. 4th Edition, IARC Lyon, 2018. p. 66-152.
2. Calkovsky V, Minarikova E, Bobrovska M, Hajtman A. Malignant melanoma of the neck. Acta Medica Martiniana 2008;8(3):37-44.
3. Kozarova A, Minarikova E, Pappova T. Practical use of high-resolution 20 MHZ ultrasonography in dermatovenerology. Acta Medica Martiniana 2016;16(3):22-31.
4. Minarikova E, Smolarova M, Minarik M. Activity of skin cancer clinic at Martin University Hospital in 2017. Acta Medica Martiniana 2018;18(1):21-29.
5. Barnhill RL, Sarantopoulos GP, Gupta K. Less common variants of cutaneous melanoma. In: Sharfman WH, Abraham J. Melanoma (Emerging Cancer Therapeutics, Vol. 3, Issue 3), 1st Edition. Demos Medical, 2012, p. 421-460.
6. Busam KJ. Dermatopathology. A Volume in the Series: Foundations in Diagnostic Pathology. 1st Edition. Saunders Elsevier, 2010, p. 478.
7. Magro CM, Crowson AN, Mihm MC jr. Unusual variants of malignant melanoma. Modern Pathology 2006;19:S41-70
8. Adamicova K, Fetisovova Z, Bobrovska M, Homola I. The importance of using SOX10 for exact diagnosis of desmoplastic melanoma. Acta Medica Martiniana 2019;19(3):112-116.

9. Xu Z, Shi P, Yibulayin F, et al. Spindle cell melanoma: Incidence and survival, 1973-2017. Oncol Lett 2018;16(4):5091-5099.
10. Weissinger SE, Keil P, Silvers DN, et al. A diagnostic algorithm to distinguish desmoplastic from spindle cell melanoma. Mod Pathol 2014;27(4):524-534
11. Smolarova M, Minarikova E. Dermoscopy as a valuable tool in diagnosis of nodular amelanotic melanoma and nodular basal cell carcinoma. Acta Medica Martiniana 2017;17(1):21-27.
12. Ohsie SJ, GP Sarantopoulos, Cochran AJ, Binder SW. Immunohistochemical characteristics of melanoma. J Cutan Pathol 2008;35(5):433-444.
13. Busam KJ, Kucukgol D, Sato E, et al. Immunohistochemical analysis of novel monoclonal antibody PNL2 and comparison with other melanocyten differentiation markers. Am J Surg Pathol 2005;29(3):400-406.
14. Grzywa TM, Pascal W, Wlodarski PK. Intratumor and intertumor heterogeneity in melanoma. Transl Oncol 2017;10(6):956-975.
15. Cheng L, Lopez-Beltran A, Massari F, et al. Molecular testing for BRAF mutations to inform melanoma treatment decisions: a move toward precision medicine. Mod Pathol 2018; 31(1):24-38.

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