VOL. 4 (7). ISSN 2424-5755
2020 05 30

RADIOLOGY UPDATE

JOURNAL available at radiologyupdate.org

This page is intentionally left blank

Editorial board

This page is intentionally left blank

CONTENTS

Pathological changes in non-contrast CT scans, safety, and outcome differences in patients with elevated INR compared to patients with normal INR after acute ischemic stroke treatment with mechanical thrombectomy

Domas Bajerūnas[1], Kotryna Mockaitytė[1], Andrius Pranculis[2], Algidas Basevičius[3]

1 Lithuanian University of Health Sciences, faculty of Medicine, Kaunas, Lithuania
2 Hospital of Lithuanian University of Health Sciences, department of Interventional Radiology, Kaunas, Lithuania
3 Hospital of Lithuanian University of Health Sciences, department of Radiology, Kaunas, Lithuania

ABSTRACT

Background and aim: Stroke is the second main reason for death worldwide [1]. Patients with atrial fibrillation have an increased ischemic stroke risk. Therefore, they are anticoagulated to reduce thromboembolic event chance [2]. Although anticoagulation is associated with haemorrhage complications, there is little information about the safety and the outcomes of treating acute ischemic stroke with mechanical thrombectomy in patients with elevated international normalised ratio (INR) [3]. This trial aimed to find out if there are differences in safety and outcomes in patients with elevated INR when treating acute ischemic stroke with mechanical thrombectomy.

Materials and methods: 183 cases were divided into two groups: patients with INR < 1.2 and patients with INR ≥ 1.2. Age and gender distribution were evaluated. Intracranial haemorrhage and mortality rates were analysed. Four pathological changes (signs of acute ischemia, haemorrhage transformations, deformations in the ventricular system, and the midline shift) in non-contrast CT scans before the mechanical thrombectomy and 24 hours after the thrombectomy were analysed.

Results: Results revealed that there was no statistical significance between the groups in intracranial haemorrhage ($p = 0.292$) or morality ($p = 0.345$) rates. Several pathological changes before the mechanical thrombectomy ($p = 0.631$) and 24 hours after mechanical thrombectomy ($p = 0.398$) were not statistically significantly different. In 24 hours, the study group did not develop ($p = 0.548$) a statistically significant number of new pathological changes when comparing to the control group.

Conclusion: Mechanical thrombectomy safety and outcomes when treating acute ischemic stroke in patients with elevated INR did not differ from patients who had regular INR.

Keywords: Acute ischemic stroke, non-contrast CT, mechanical thrombectomy, safety, elevated INR.

1. INTRODUCTION

Each year stroke is the second main reason for death worldwide [1]. According to the latest available statistics in Europe (2016), the number of noncommunicable diseases is increasing [4]. Mainly, stroke and ischemic heart disease caused around 15.2 million deaths worldwide in 2016 [4]. Although the absolute mortality from stroke has a downtrend due to improvements in diagnostics and therapy, the absolute number of people who have a stroke every year is increasing [5,6].

There are two main types of stroke – ischemic and haemorrhagic. Only about 13% of all strokes are haemorrhagic [7]. They occur when there is extravasation due to a defect in the vessel wall. When comparing mortality, haemorrhagic stroke (68%) has a higher death rate than ischemic stroke (57%) [8]. Ischemic stroke accounts for 87% of all strokes, and this type is usually caused by atherosclerosis and thromboembolic events when the middle cerebral artery is occluded with thrombi [9]. Even though ischemic stroke is responsible for fewer deaths than haemorrhagic stroke, according to other sources, it is the leading long term disability causing disease [10,11]. It is thought that by the year 2035, there will be 34% more cases of ischemic stroke worldwide when compared to the 2015 year data. This

means that the number of people who require permanent nursing will also increase [12,13].

Symptoms of ischemic stroke are usually associated with dysfunction of the brain region, in which the occluded artery is proving blood to [14]. A quick neurological deficit is one of the main ischemic stroke symptoms. Patients complain of sudden numbness or weakness in the face, arm, or leg, especially on one side of the body, speech disorder is also frequently observed.
When it comes to diagnostics, the modality of choice is a non-contrast computed tomography (CT) scan because of its full availability and speed. It is also sensitive in detecting intracerebral haemorrhage, which can be found when a haemorrhagic stroke occurs [15]. This is very important because of entirely different treatment tactics. The main objective of ischemic stroke treatment is the administration of intravenous thrombolysis and mechanical thrombectomy, while in the case of haemorrhagic stroke, the main treatment aspects are systolic blood pressure control and discontinuation of anticoagulants [16,17].

In the early stages of ischemic stroke, pathological findings in non-contrast CT can be minor and difficult to detect. According to other authors, we can see these pathological findings in the scans: hypodense ischemic area, hyperdense middle cerebral artery, loss of grey-white differentiation, cortical swelling, and loss of sulcation [18]. Midline shift, which can occur due to cerebral oedema, cerebral ventricle deformation, and haemorrhagic transformation, is associated with worse patient outcomes [19,20].
When an acute ischemic stroke is suspected, the main objective is to restore blood flow as quickly as possible. All the necessary diagnostic procedures: non-contrast CT scan, blood oxygenation, glucose levels, international normalised ratio (INR), and an electrocardiogram – must be performed within 60 minutes of the patient reaching the hospital [17,21]. Intravenous thrombolysis must be performed within 4,5 hours from the first symptom onset time because studies have shown that after this therapeutic window, intravenous Alteplase becomes ineffective [17]. If occlusion of a large vessel causes the stroke, there is little chance that thrombolysis will be useful, in this case, mechanical thrombectomy becomes the primary treatment choice. This endovascular procedure is accomplished by aspirating thrombus with stent retrievers [22]. According to the newest recommendations, mechanical thrombectomy should be performed within 6 hours from the first symptom onset [17].

When we talk about ischemic stroke, a significant factor is an atrial fibrillation [22]. Our society is getting older, and atrial fibrillation numbers are increasing [4,23]. According to other sources, patients with atrial fibrillation have five times increased risk of developing an ischemic stroke while comparing to the rest of the population in the same age group [2]. This is because people with atrial fibrillation have an increased risk of thromboembolic complications due to the pathological formation of thrombus in the atriums [2]. To reduce the risk of these complications, patients are getting anticoagulated [2]. It is known that anticoagulation increases the risk of intracranial haemorrhage, which is also one of the mechanical thrombectomy complications associated with worse patient prognosis [3,24].

Many studies have proven that mechanical thrombectomy is a safe and effective method for treating acute ischemic stroke [25–28]. On the other hand, previously mentioned studies have not involved anticoagulated patients in their study groups. Does this pose a question, is mechanical thrombectomy safe to these patients? Also, there is little information about the safety and outcomes of performing mechanical thrombectomy on patients with elevated INR. Therefore, this research aimed to investigate if there is a significant difference in safety, outcomes, and non-contrast CT scan pathological changes between patients with elevated INR and patients with regular INR.

2. MATERIALS AND METHODS

We performed a retrospective study of 183 patients based on the data from the Lithuanian University of Health Sciences Hospital (LUHSH)

Kauno Klinikos electronic registry. Case-reports in 2014 January and 2018 January were analysed. Data about patient age, gender, INR, intracranial haemorrhage rate, mortality was recorded. Also, non-contrast CT scans before mechanical thrombectomy and 24 hours after mechanical thrombectomy were analysed. The study was approved by the Bioethics Committee of the LUHS (No. BEC-MF-210).

Firstly, the research was performed in these databases: PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Wiley Online Library (https://onlinelibrary.wiley.com), Science Direct (https://www.sciencedirect.com). Keywords were used: acute ischemic stroke, stroke diagnostics, ischemic stroke CT signs, mechanical thrombectomy safety, patients with elevated INR, acute ischemic stroke treatment.

The study group included 55 patients who met these inclusion criteria:
• Patients who had an acute ischemic stroke and were treated with mechanical thrombectomy at LUHSH Kauno Klinikos Interventional Radiology unit.
• Patient INR was ≥ 1.2.
• Non-contrast CT scans were performed at the LUHSH Kauno Klinikos Radiology department.
• The patient had a non-contrast CT scan performed before mechanical thrombectomy and 24 hours after the treatment.
• No cerebral anomalies were found in non-contrast CT scans.

The control group included 128 patient who met these inclusion criteria:
• Patients who had an acute ischemic stroke and were treated with mechanical thrombectomy at LUHSH Kauno Klinikos Interventional Radiology unit.
• Patient INR was < 1.2.
• Non-contrast CT scans were performed at the LUHSH Kauno Klinikos Radiology department.
• The patient had a non-contrast CT scan performed before mechanical thrombectomy and 24 hours after the treatment.
• No cerebral anomalies were found in non-contrast CT scans.

Study and control group patient distribution by age and gender was compared. We analysed if patients with elevated INR have a higher intracranial haemorrhage and mortality rate.

Non-contrast CT scans were performed in the study and control group patients. We looked for four pathological findings: signs of acute ischemia, haemorrhage transformations, deformations in the ventricular system, and the midline shift ≥ 0.5 cm. These pathological findings were associated with further patient prognosis. Each finding was equivalent to a score of "1: if it was present. "0" was given if the pathological finding was absent. Non-contrast CT scan findings before mechanical thrombectomy were analysed to see if both groups had similar pathological changes when they arrived at the hospital. We analysed changes 24 hours after the procedure to predict the outcome of the patient. Bucker et al. supported this idea., who stated that both the 24-hour and 1-week ischemic lesions were similarly significantly associated with functional outcome (both $p < 0.001$) [29]. We also looked at how many new changes were developed by the patients in a period of 24 hours. This was accomplished by subtracting the number of changes before the procedure out of the number of changes 24 hours after the procedure. All the non-contrast CT scans were analysed with a radiologist ensuring the quality of the final results.

Statistical analysis was performed with "SPSS (Statistical Package for the Social Sciences) program 23.0" ("IBM," Armonk, New York, USA) and "Microsoft Excel 2019" ("Microsoft Corporation," Redmond, Washington, USA") programs. To calculate statistical significance, an analysis of covariance (ANCOVA) with age as a covariate was performed. Levene's test was used to test if the groups were homogenous. Pearson chi-square ($\chi 2$) tests were used to calculate the frequency of categorical variables. Summarised statistics were used for: value means, standard deviation, maximum and minimum values. The observed differences were considered statistically significant when the calculated significance level (p-value) was lower than the selected significance level ($\alpha = 0.05$).

3. RESULTS

In the study, we observed 183 cases of patients aged 40-85 diagnosed with acute ischemic stroke and treated with mechanical thrombectomy. The study group consisted of 55 patients: 33 (60%) males and 22 (40%) females. The age means of males in the study group was 72.41 (SD = 5.55) years, females – 73.42 (SD = 6.43) years. The age mean by gender did not differ statistically significantly (p = 0.372) in the study group. The control group consisted of 128 patients, 60 (46.88%) males, and 68 (53.12%) females. The age means of males was 71.32 (SD = 6.64) years; the age mean of females was 73.45 (SD = 6.08) years. The age mean by gender did not differ statistically significantly (p = 0.442) in the control group. While comparing both groups, the age means of the study group 72.91 (SD = 6.48) years was not statically significantly higher (p = 0.232) than the age means of the control group 72.02 (SD = 7.46) years. The data is presented in Table 1.

Table 1. Study and control group patient distribution by age and gender

	Study group (N=55)	Control group (N=128)
Age		
Male, age mean (SD)	72.41 (5.55)	71.32 (6.64)
Female, age mean (SD)	73.42 (6,43)	73.45 (6.08)
Total, age mean (SD)	72.91 (6.48)	72.02 (7.46)
Gender		
Male, N (%)	33 (60)	60 (46.88)
Female, N (%)	22 (40)	68 (53.12)

The incidence of intracranial haemorrhage was not statistically significantly higher in the study group (p = 0.292) than in the control group. When comparing mortality rate, death occurred to 8 (14.54%) patients in the study group and to 23 (17.96%) patients in the control group, but this difference was not statically significant (p = 0.345). The data is summarised in Table 2.

Table 2. Study and control group intracranial haemorrhage and mortality rates

	Study group (N = 55)	Control group (N = 128)
Intracranial haemorrhage		
Present, N (%)	31 (56.36)	62 (48.44)
Absent, N (%)	24 (43.64)	66 (51.56)
Mortality		
Died, N (%)	8 (14.54)	23 (17.96)
Survived, N (%)	47 (85.46)	105 (80.04)

First, we calculated that there was no statistical significance in non-contrast CT scans before thrombectomy between anticoagulated patients and patients with normal INR (p = 0.631). Patient group with normal INR non-contrast CT scan sum mean was 0.54 (SD = 0.614) compared to anticoagulated group 0.49 (SD = 0.635). From this, we can say that both groups had roughly the same number of pathological changes before mechanical thrombectomy treatment.

Next, we did not find statistically significant differences between the groups in non-contrast CT scans 24 hours after mechanical thrombectomy (p = 0.398). The patient group with normal INR had an average number of 2.05 (SD = 1.260) pathological changes, while the elevated INR group patients had an average number of 1.97 (SD = 1.177) pathological changes.

Also, the study group did not show significant pathological changes score difference in developing new pathological changes over 24 hours between the two CT scans (p = 0.548). The study patient group developed around 1.75 (SD = 1.324) new pathological changes in 24 hours, while the control group around 1.82 (SD = 1.139) new pathological changes. The data is presented in Fig. 1.

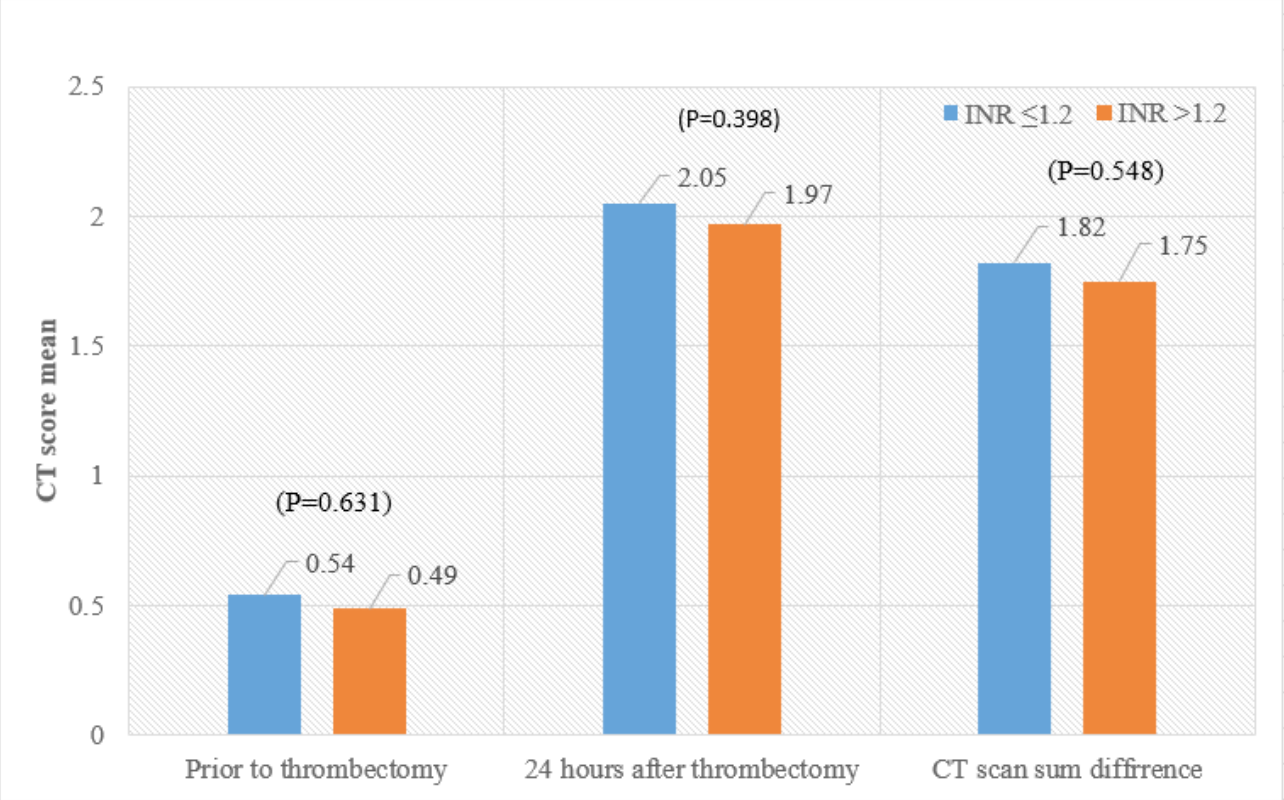


Fig. 1. Non-contrast CT score mean diversity before the thrombectomy, 24 hours after the thrombectomy and new changes over 24 hours

4. DISCUSSION

This study showed that the safety of acute ischemic stroke treated with mechanical thrombectomy statistically significantly different between patients with normal blood clotting and anticoagulated patients. The number of pathological changes in non-contrast CT scans, the frequency of intracranial is no haemorrhage, and mortality did not differ between the two groups. This result supports the safety of mechanical thrombectomy independent of the patient's blood clotting.

Some authors have been investigating whether antiplatelet agents may increase the risk of haemorrhagic stroke. Garcia-Rodriguez et al. [24] studied patients who were taking aspirin or warfarin. This study found that aspirin use was not associated with an increased risk of intracranial haemorrhage. Patients who took aspirin daily for over three years even had a reduced risk of subarachnoid haemorrhage. In contrast to aspirin, warfarin users had a significantly higher risk of intracranial haemorrhage and a moderately increased risk of subarachnoid haemorrhage. Our study did not analyse which antiplatelet agent or anticoagulant the patient was taking, but, in contrast to the Garcia-Rodriguez [24] study, our group of anticoagulated patients did not have a significantly higher incidence of intracranial

haemorrhage. Our sample size was significantly smaller, only 183 patients, compared to the 3131 cases analysed in the recently mentioned work [24], which could have led to different results.

In 2016, a study was conducted to analyse the safety of mechanical thrombectomy when treating acute ischemic stroke in patients who were taking vitamin K antagonists. Uphaus et al. [30] collected data from 815 patients and concluded from the results that the use of vitamin K antagonists was not associated with worse clinical outcomes or an increased risk of intracranial haemorrhage. Although this contradicts to the results obtained by Garcia-Rodriguez et al. [24], we have to keep in mind that Garcia-Rodriguez investigated the association of intracranial haemorrhage risk with the use of vitamin K antagonists in the general population, rather than among patients who received endovascular treatment after an ischemic stroke. Our results support the results obtained by Uphaus et al., that mechanical thrombectomy safety and outcomes are not associated with patient INR.

Rebello et al. [31] conducted a prospective study in patients with ischemic stroke who were treated endovascularly. After collecting 297 cases of patients with INR 1.7–2.0 between 2010 and 2015, they analysed petechial haematomas, procedure success, and 90-day functional outcomes. This study is similar to ours because it did not track, which anticoagulant the patient was taking. Study calculations showed that neither demographics, safety, or efficacy differed between the groups. No statistically significant changes were observed when comparing mortality, which also supports our findings.

Seiffge et al. [32] searched about the relation between patient blood coagulation and outcomes after acute ischemic stroke. Their study was about the impact of prior treatment with novel oral anticoagulants on bleeding complications and outcomes. They stated that the safety of intravenous thrombolysis or endovascular treatment is the same in patients receiving subtherapeutic vitamin K antagonist treatment or novel oral anticoagulants when comparing with those without prior anticoagulation. Although in our study, we did not track what anticoagulant patients were taking, Seiffge et al., conclusions support our ones.

There were some limitations in our study. First, the results might be controversial because of the small sample size. Also, both groups were not equal in the number of patients. Furthermore, types of anticoagulants were not taken into perspective as well as the type of anaesthesia during the mechanical thrombectomy. Studies have shown that general anesthesia could be associated with worse outcomes after endovascular treatment [33]. Lastly, this is a retrospective study in a single-centre, therefore our results need to be further validated in a large scale, multi-centre study.

Based on these analysed studies, we can say that decreased blood clotting is not a contraindication to treat ischemic stroke with mechanical thrombectomy. Our work was mainly based on the changes seen in the non-contrast CT scan images; this type of analysis method is not described in either Lithuanian or foreign literature. However, the results we obtained were similar to those of other authors, so this method can be considered correct and further proves that endovascular treatment is a safe, minimally invasive approach for treating ischemic stroke regardless of the patient's INR.

5. CONCLUSIONS

After analysing results, we could say that mechanical thrombectomy safety and outcomes when treating acute ischemic stroke in patients with elevated INR did not differ from patients who had regular INR. Intracranial haemorrhage, mortality rate, and several pathological changes in non-contrast CT scans were not statistically significantly different between patient groups with different INR.

6. ACKNOWLEDGEMENTS AND DISCLAIMERS

No funding was received for this research.

REFERENCES

1. Wang H, Naghavi M, Allen C, Barber RM, Carter A, Casey DC, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;120(3):439–48.

2. Reiffel JA. Atrial fibrillation and stroke: epidemiology. Am J Med. 2014;127(4):15–6.

3. Neuberger U, Kickingereder P, Schönenberger S, Schieber S, Ringleb PA, Bendszus M, et al. Risk factors of intracranial hemorrhage after mechanical thrombectomy of anterior circulation ischemic stroke. Neuroradiology. 2019;61(4):461–9.

4. Katan M, Luft A. Global Burden of Stroke. Semin Neurol. 2018;38(2):208–11.

5. Townsend N, Nichols M, Scarborough P, Rayner M. Cardiovascular disease in Europe - Epidemiological update 2015. Eur Heart J. 2015;36(40):3182–3.

6. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990-2010: Findings from the Global Burden of Disease Study 2010. Lancet. 2014;383(9913):245–55.

7. Gomes J, Wachsman AM. Types of strokes. In: Handbook of Clinical Nutrition and Stroke. 2013. p. 15–31.

8. Koton S, Schneider ALC, Rosamond WD, Shahar E, Sang Y, Gottesman RF, et al. Stroke incidence and mortality trends in US communities, 1987 to 2011. JAMA - J Am Med Assoc. 2014;312(3):259–68.

9. Schoen FJ, Mitchell, RN. Robbins & Cotran Pathologic Basis of Disease. In: Robbins & Cotran Pathologic Basis of Disease. New York: Saunders; 2015. p. 345–56.

10. World Health Organization. The top 10 causes of death [Internet]. 2018 [cited 2019-02-27]. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death/.

11. Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2197–223.

12. Stevens E, Emmett E, Wang Y, McKevitt C, Wolfe C. The burden of stroke in Europe. Stroke Alliance for Europe. 2017. 6–36 p.

13. Furie B, Furie BC. Mechanisms of thrombus formation. N Engl J Med. 2008;359(9):938–49.

14. Yew KS, Cheng EM. Diagnosis of acute stroke. Am Fam Physician. 2015;91(8):528–36.

15. Caplan LR. Caplan's Stroke: A Clinical Approach: Fourth Edition. 4th edition. Caplan's Stroke: A Clinical Approach: Fourth Edition. Boston, USA: Saunders; 2009. 1–656 p.

16. Hemphill JC, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the Management of Spontaneous Intracerebral Hemorrhage. Stroke. 2015;46(7):2032–60.

17. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke A Guideline for Healthcare Professionals From the American Heart Association/American Stroke A. Stroke. 2019;49(3):15.

18. Merino JG, Warach S. Imaging of acute stroke. Nat Rev Neurol. 2010;6(10):560–71.

19. Ferdian E, Boers AM, Beenen LF, Cornelissen BM, Jansen IG, Treurniet KM, et al. Automated ventricular system segmentation in ct images of deformed brains due to ischemic and subarachnoid hemorrhagic stroke. In: Lecture Notes in Computer Science (including subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics). 2017. p. 149–57.

20. Liao CC, Chen YF, Xiao F. Brain midline shift measurement, and its automation: A review of techniques and algorithms. International Journal of Biomedical Imaging. 2018. p. 1–13.

21. Sauser K, Bravata DM, Hayward RA, Levine DA. A national evaluation of door-to-imaging times among acute ischemic stroke patients within the veteran's health administration. J Stroke Cerebrovasc Dis. 2015;24(6):1329–32.

22. Capriotti T, Murphy T. Ischemic Stroke. Home Health Now. 2016;34(5):259–66.

23. Morillo CA, Banerjee A, Perel P, Wood D, Joven X. Atrial fibrillation: The current epidemic. J Geriatr Cardiol. 2017;14(3):195–203.

24. García-Rodríguez LA, Gaist D, Morton J, Cookson C, González-Pérez A. Antithrombotic drugs and risk of hemorrhagic stroke in the general population. Neurology. 2013;81(3):566–74.

25. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, et al. SolitaireTM with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial: Protocol for a randomised, controlled, multi-centre study comparing the Solitaire revascularisation device with IV tPA with IV t. Int J Stroke. 2015;10(3):439–48.

26. Jovin TG, Chamorro A, Cobo E, De Miquel MA, Molina CA, Rovira A, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372(24):2296–306.

27. Demchuk AM, Goyal M, Menon BK, Eesa M, Ryckborst KJ, Kamal N, et al. Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimising CT to recanalisation times (ESCAPE) trial: Methodology. Int J Stroke. 2015;10(3):429–38.

28. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, et al. thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med. 2018;378(8):708–18.

29. Bucker A, Boers AM, Bot JCJ, Berkhemer OA, Lingsma HF, Yoo AJ, et al. Associations of Ischemic Lesion Volume with Functional Outcome in Patients with Acute Ischemic Stroke: 24-Hour Versus 1-Week Imaging. Stroke. 2017;48(5):1233–40.

30. Uphaus T, Singer OC, Berkefeld J, Nolte CH, Bohner G, Niederkorn K, et al. Safety of endovascular treatment in acute stroke patients taking oral anticoagulants. Int J Stroke. 2017;12(4):412–5.

31. Rebello LC, Haussen DC, Belagaje S, Anderson A, Frankel M, Nogueira RG. Endovascular treatment for acute ischemic stroke in the setting of anticoagulation. Stroke. 2015;26(13):3536–9.

32. Seiffge DJ, Hooff R-J, Nolte CH, Béjot Y, Turc G, Ikenberg B, et al. Recanalization Therapies in Acute Ischemic Stroke PatientsCLINICAL PERSPECTIVES. Circulation. 2015;132(13):1261–9.

33. Campbell BCV, van Zwam WH, Goyal M, Menon BK, Dippel DWJ, Demchuk AM, et al. Effect of general anaesthesia on functional outcome in patients with anterior circulation ischaemic stroke having endovascular thrombectomy versus standard care: a meta-analysis of individual patient data. Lancet Neurol. 2018;17(1):47–53.

The role of imaging modalities in diagnostics of posterior paravertebral mediastinal pathologic changes

Dovilė Barakauskaitė[1], Simas Giedrys[1], Ieva Keturkaitė[1], Kamilė Pocepavičiūtė[1], Laima Dobrovolskienė[1]

[1] *Department of Radiology of Lithuanian University of Health Sciences Kaunas, Lithuania.*

ABSTRACT

Background: Different paravertebral pathologies in posterior mediastinum may cause diagnostic difficulties. Usually, the symptoms are not specific, and the changes are found during routine investigations. In roentgenograms, they do not have specific features so more accurate imaging modality must be chosen to define whether it is benign or malignant. This can be made by using a CT or MRI scan. It is crucial to choose the right strategy for each pathology, as the aim of imaging may vary in different situations. The aim of our study was to evaluate and compare the features of pathological findings in the posterior mediastinum.

Materials and methods: We performed the retrospective observational study at LUHS hospital Kauno Klinikos Radiology clinic. Medical health records and x-ray, CT and MRI radiologic view made between 2015 and 2019 were analyzed. Patients who underwent CT and MRI scanning repeatedly for clarification of diagnosis were investigated PET/CT or were operated for histological confirmation of diagnosis and who had pathologic findings in posterior mediastinum were selected.

Results: The study consisted of 81 patients with verified posterior mediastinal masses. A variety of clinical diagnoses were confirmed, 70,4% (n = 57) of the masses were oesophagal tumours, and the remaining cases consisted of benign cysts and other cysts like lesions. Oesophagal tumours were most commonly located in the middle thoracic part of the oesophagus and presented itself as a circular wall thickening with a homogenous structure and a rare rate of local invasion of adjacent structures. There was a statistically significant difference between attenuation on CT scan before and after the administration of intravenous contrast medium (p<0,001). The majority of cystic masses 66,7% (n=16) presented with a well-defined circumscribed border on a conventional radiograph. CT images showed that 79,2% (n=19) masses were heterogeneous and had a various degree of contrast enhancement. In diffusion-weighted magnetic resonance imaging, ADC values was measured with an average of 1,86 0,99 * 10-3mm2/s. PET/CT showed hypermetabolism in 41,7% (n=10) of the masses and possibly benign, no metabolic changes in the remaining 58,3% (n=14). There was no statistically significant difference in mean attenuation measured on CT between metabolically active and inactive masses (p=0,546). There was a statistically significant difference in apparent diffusion coefficient between metabolically active and inactive masses (p=0,005).

Conclusion: Conventional chest radiography can be helpful to define the anatomical location, borders and size of the masses. Multislice computed tomography can help to obtain information about densities and CE of the lesion. In different sequences of MRI masses have an isointense or hyperintense signal which provides additional information about the inner structure of lesion. Apparent diffusion coefficient (ADC) in MRI can be helpful distinguishing malignant from benign masses.

Keywords: computed tomography, magnetic resonance imaging, posterior mediastinum

INTRODUCTION

Posterior mediastinum is the anatomical region that contains a variety of structures such as the descending thoracic aorta, oesophagus, azygos and hemiazygos veins, thoracic duct, lymph nodes, adipose tissue, vagus and splanchnic nerves, and autonomic ganglia. Due to this, the range of pathologies in this region may be broad. Masses of the mediastinum are usually found incidentally during routine chest investigations [1]. In roentgenograms, they appear as rounded lesions with increased opacity, and 40.7% of cases are asymptomatic [1]. Symptoms arise from the compression on mediastinal structures, but they are not specific. These include dyspnea, chest pain, cough and dysphagia [1].

The main goal of investigating these cases is to

identify whether the mass in the posterior mediastinum is malignant or benign. If the process is malignant, the aim is to determine the stage. In the case of the benign process, the most important is to choose the right strategy for observing the changes during the time. Such imaging modalities as CT and MRI scan can precisely specify the localization, size, tissue characteristics and relationship with other structures.
The aim of this study was to evaluate and compare CT and MRI findings of malignant and benign pathologies in the posterior mediastinum.

BRONCHOGENIC CYSTS

Posterior mediastinum is one of the regions where bronchogenic cysts may appear [2]. In 52% of cases, they are located near carina [4]. These cysts contain mucous gland tissue and muscle [3]. The size may increase due to haemorrhage or infection [3].
On chest radiographs, they usually appear as well-defined solitary masses with homogenous opacity [2]. On CT scans, bronchogenic cysts appear as sharply marginated mediastinal masses with attenuation value varying from water to soft-tissue attenuation [5]. MRI can help to sort out the nature of cystic lesion [5]. The appearance of fluid-fluid levels seen on MRI can help to confirm the true cystic nature of bronchogenic cyst [6].

MATURE CYSTIC TERATOMA

Mature cystic teratoma is a cystic tumour that may contain skin, teeth, hair, bone, cartilage and even bronchial or gastrointestinal epithelium [2]. Only 3%-8% of these cysts are in the posterior mediastinum, while a majority of them appears in anterior mediastinum [26]. On plain chest films, they appear as sharply marginated, round or lobulated masses that extend to the one side of the midline [2]. Ossification, calcification and teeth may be apparent [7]. On CT, they are well-defined heterogeneous masses with the walls that may enhance the contrast [8]. Fluid, fat, soft tissue and calcium may be apparent [8]. On MRI, they appear as heterogeneous masses containing the same kinds of tissues, as mentioned before [9].

INTRATHORACIC MENINGOCELE

Intrathoracic meningocele is a cystic sac in the thoracic cavity that contains cerebral fluid and is formed by spinal meninges. These cystic lesions are associated with neurofibromatosis [10]. Patients without neurofibromatosis rarely develop these kinds of cysts [11].
At radiography, they present as sharply defined round, lobulated or smooth paraspinal masses [2]. At CT, intrathoracic meningoceles appear as well-defined, homogenous, low-attenuation paravertebral masses [2]. On MRI, it appears as a cystic mass with homogenous structure and connection with the spinal canal [11]. The intensity of cystic mass is similar to cerebrospinal fluid on T2 weighted images [11].

LYMPHANGIOMA

Lymphangioma is a congenital benign lesion. It is caused by the focal proliferation of lymphatic tissue with a multicystic pattern [12]. Only 10% of manifest in the thorax; meanwhile it is prevalent in the axillary region and neck [13]. Due to their soft consistency, the symptoms are rare [2]. At radiography, they usually appear as well-defined, round, lobulated masses [14]. Pleural effusions may present as well, and they may be unilateral or bilateral [2]. On CT, they usually appear as smooth lobulated mass [14]. They can have both low and high attenuation, depending on cystic content [2].
On MRI, at T1-weighted images, they have similar or higher signal than muscle [15]. On T2-weighted images, high signal intensity is characteristic due to the cystic substance [15].

NEURENTERIC CYST

Neurenteric cysts are rare and may have a connection with meninges [14]. They are composed of heterotopic endodermal tissue and are associated with abnormalities of the spine [16]. The symptoms usually appear due to the compression of the spinal cord and associated nerve roots [16]. CT is suitable for evaluating vertebral abnormalities. However, MRI is superior in defining the nature of these structures [17]. MRI findings are isointense lesions in T1-weighted

images and hyperintense lesions on T2-weighted images [18]. Also, MRI is the most suitable imaging modality for long-term follow-up as the recurrence is characteristic [17]. MRI is accepted to be the gold standard for defining neurenteric cysts [16].

CYSTLIKE LESIONS

Some of the pathologies may go through cystic degeneration and appear as mixed cystic and solid structures on CT and MRI [2]. In general, these changes include Hodgkin disease, mediastinal carcinomas, malignant lymphoma and metastases [2, 19, 20]. Radiation therapy and chemotherapy may induce these lesions [2]. On CT, cystic changes have low attenuation, complex structure with a fluid like areas [20]. However, in some cases, findings may be equivocal, and diffusion MRI technique may be useful in differentiating between malignant and benign pulmonary masses [21]. The conclusion can be made by calculating the mean apparent diffusion coefficient (ADC) value [22]. The sensitivity of this technique is 90% and specificity - 100% [22]. Greater than 5mm nodules can be differentiated while using ADC value as well [23].

OESOPHAGAL TUMORS

Adenocarcinoma and squamous cell carcinoma are the most common types of oesophagal cancer. At an early stage, it may be asymptomatic. Tumour extension to mediastinum can cause chest pain. The first method for diagnosing oesophagal cancer is endoscopy with biopsy. CT scan is the modality of choice to determine TNM staging, and it helps diagnose local mediastinal invasion [24]. MRI is not routinely used for oesophagal cancer staging though it has potential to improve staging [25].

METHODS AND MATERIALS

We performed a retrospective observational study at Kaunas Clinics. Kaunas Regional Biomedical Research Ethics Committee (KRBRE) approved the study protocol and waived informed consent. In this study, medical health records made between 2015 and 2019 were analyzed. We selected patients medical records who underwent X-ray, CT and MRI scan for suspected posterior mediastinal pathology. CT scans were performed with Toshiba Aquilion One 320 slice equipment, using 120 kV, high resolution scanning with 0,5 mm slice thickness. Before the oesophagal part was scanned, the patient had to take 50 - 100 ml contrast medium per orally, and the other had intravenous contrast material. MRI scans were performed using 1.5T (Siemens Aera) or 3T (Philips Ingenia) scanners. VIBE, HASTE, BLADE TIRM, STIR sequences were used. The gold standard for diagnosis were PET/CT conclusion, histological confirmation or absence changes of the benign lesion in repeatedly CT or MRI view. Description of CT, MRI and PET/CT scans were reviewed and compared retrospectively from the medical health records. Statistical analysis of selected data was performed using "Microsoft® Excel" and statistical package "SPSS for Windows 26.0". Descriptive statistics are provided by the mean and standard deviation (M ± SD) or percentages. The distribution of quantitative traits, according to the Gaussian distribution, was checked using the Shapiro-Wilk or Kolmogorov-Smirnov criteria. The averages of the two dependent samples were compared using Student's T criteria. Differences between two independent samples were compared using the Mann-Whitney U Test.

RESULTS

1) Demographic and clinical characteristics

The study consisted of 81 patients with verified posterior mediastinal masses. The majority of participants, 74,1% (n = 60) were male and 25,9% (n = 21) were female, with a male:female ratio of 2,86:1. Patient's age ranged from 28 to 88 with the average age of 62,52 12,14. A variety of clinical diagnoses were confirmed, 70,4% (n = 57) of the masses were esophageal tumors out of which 89,5% (n = 51) were squamous cell carcinoma, 8,8% (n = 5) adenocarcinoma and 1,8% (n=1) primary melanoma of the esophagus. 29,6% (n = 24) of the cases consisted of benign cysts and other cyst like lesions. By origin 20,8% (n = 5) of the cysts were bronchogenic, 8,3%(n= 2) were neurenteric cysts, 8,3%(n= 2)

cases were confirmed as mature cystic teratoma, 4,2% (n = 1) as meningocele and 4,2% (n = 1) as lymphangioma. 54,2% (n = 13) were other cyst like lesions, which were identified by histological examination as neurogenic tumors, primary pulmonary adenocarcinoma, lymphoma, hemartoma and distant metastases.

2) Computed tomography imaging of oesophagal tumours

All of the patients who were diagnosed with oesophagal tumours had undergone chest and abdominal CT examination. Mean thickness of the oesophagus wall was measured 15,39 7,17mm, and mean tumour length was 6,34 2,66cm. The average attenuation (Hounsfield Units) before the administration of intravenous contrast medium was 30,8 10,31 Hu, and after intravenous contrast medium was injected, the average attenuation was 65,68 24,25 Hu. (Fig 1.)

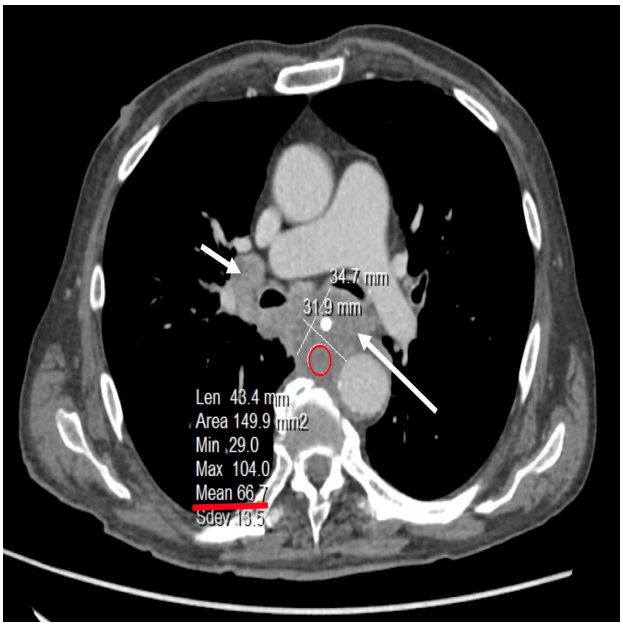


Fig.1 51-year patient's CT axial slice with CE demonstrate pathologic oesophagal masses and pathologic lymph nodes conglomerate below bifurcation (arrows). ROI (red ring) shows mean of attenuation 66,7 Hu after CE.

There was a statistically significant difference between attenuation before and after the administration of intravenous contrast medium ($p<0,001$).

The examination of CT images showed circular oesophagal wall thickening in 57,9% (n=33) of the cases and asymmetrical, eccentric thickening in remaining 42,1% (n=24) cases. The fat stranding was seen in 61,4 (n=35) of the cases. The majority 77,2% (n=44) of oesophagal masses had homogenous structure; however, after the administration of intravenous contrast medium 52,6% (n=30) showed nonhomogeneous enhancement of the tumour. The most common location of squamous cell carcinoma was the middle thoracic oesophagus, and adenocarcinoma was most prevalent in the lower part of the thoracic oesophagus (Fig. 1). 14,04% of the cases showed evident local invasion of adjacent structures with 75% (n=6) being a tracheobronchial tree and 25% (n=2) invasion into the aorta.

Fig 2. Location and histology of oesophagal masses

Location	Squamous cell carcinoma		Adenocarcinoma	
	n	%	n	%
Upper thoracic part	9	17,65%	0	0
Middle thoracic part	26	50,98%	1	20%
Lower thoracic part	16	31,37%	4	80%

3) The multimodal approach to imaging of cystic posterior mediastinal masses

A conventional frontal and lateral chest radiograph was performed for 29,6% (n = 24) of patients and examined to determine the anatomical location, borders and size of the masses. The mean diameter of the masses was 4,87 2,26cm with a minimum of 1,5cm and maximum of 9,2cm. The majority of the masses 66,7% (n=16) presented with a well-defined circumscribed border, and remaining cases showed sharply marginated, ill-defined borders (Fig.3)

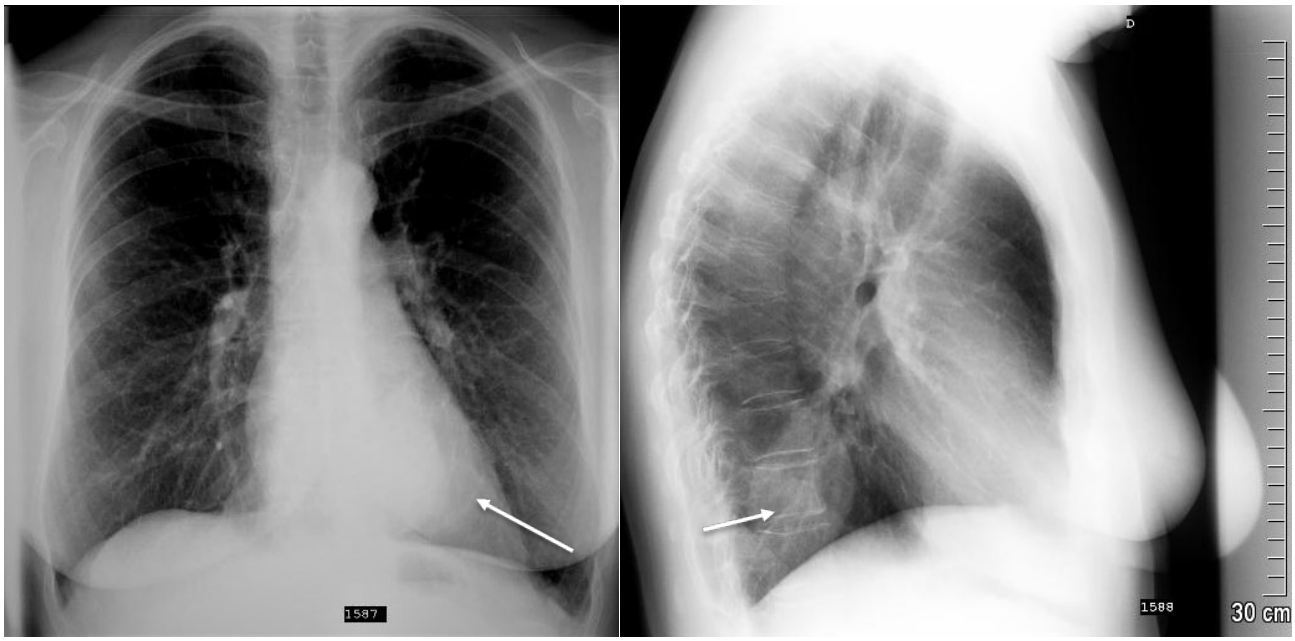


Fig.3 29-year patient's chest PA (a) and lateral (b) x-rays demonstrate (arrows) left lower paravertebral ill-defined pathologic masses.

Fig 4. Location of cystic masses by side and segment of the masses epicentre

Location	segment 1		segment 2		segment 3	
Left side	9	37,5%	0	0%	3	12,5%
Right side	7	29,17%	5	20,83%	0	0%

Multislice computed tomography and magnetic resonance imaging scan were performed to obtain more detailed information. CT images showed that 79,2% (n=19) masses had heterogeneous structure and 20,8% (n=5) were homogenous. After administration of intravenous contrast medium, 33,3% (n=8) showed no enhancement and had mean attenuation of 47,25 7,72Hu. 20,8% (n=5) masses showed slight enhancement, 29,2% (n=7) borderline enhancement and 16,7% (n=4) showed intense enhancement with average attenuation of 48 4,19Hu (Fig.5).

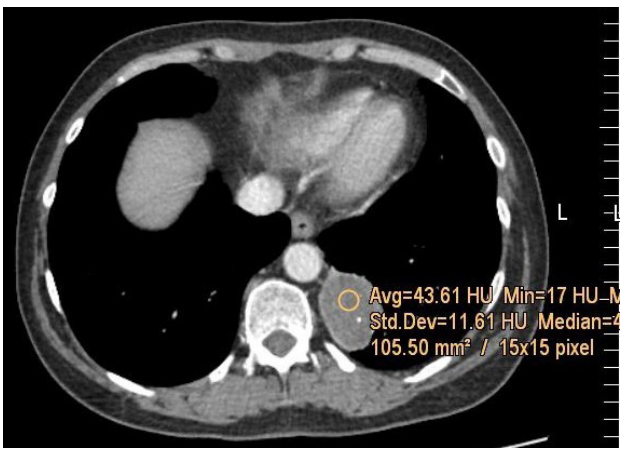


Fig.5. 29-year patient's CT axial scan after CE demonstrate (arrow) left paravertebral ill-defined homogeneous cystic lesions with 43 HU attenuation (ROI).

MRI HASTE sequence showed signal isointensity in 45,8% (n=11) of the cases, hyperintensity in 54,2% (n=13) and not a single case of hypointense signal when compared to muscle tissue signal (Fig.6). MRI TIRM sequence showed signal hypointensity in 25% (n=6), isointensity in 37,5% (n=9) and hyperintensity in 37,5% (n=9). In diffusion-weighted magnetic resonance imaging apparent diffusion coefficient (ADC) was measured with an average of 1,86 0,99 x10-3mm2/s with a minimal value of 0,8 x 10-3 mm2/s and maximum value of 3,6 x 10-3mm2/s (Fig.7 a,b).

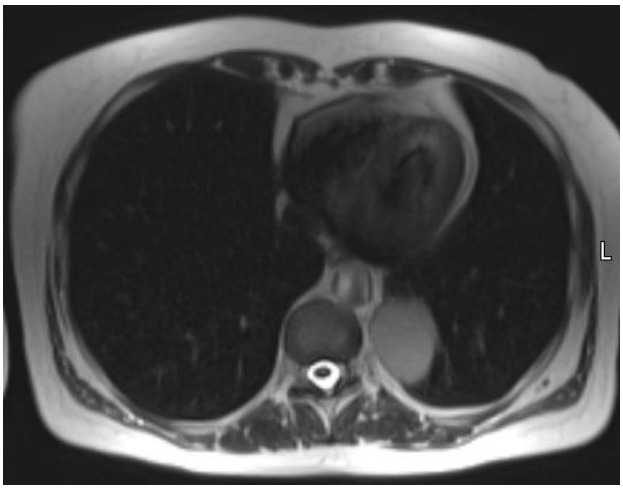


Fig.6. 29-year patient's HASTE axial MRI view shows signal hyperintensity in the oval left paravertebral lesion (arrow).

Fig.7. 29-year patient's MRI TIRM coronal (a) view shows (arrow) signal hypointensity in oval left paravertebral lesion, and DWI axial slice ROI shows high 2,1 x 10-3mm2/s ADC.

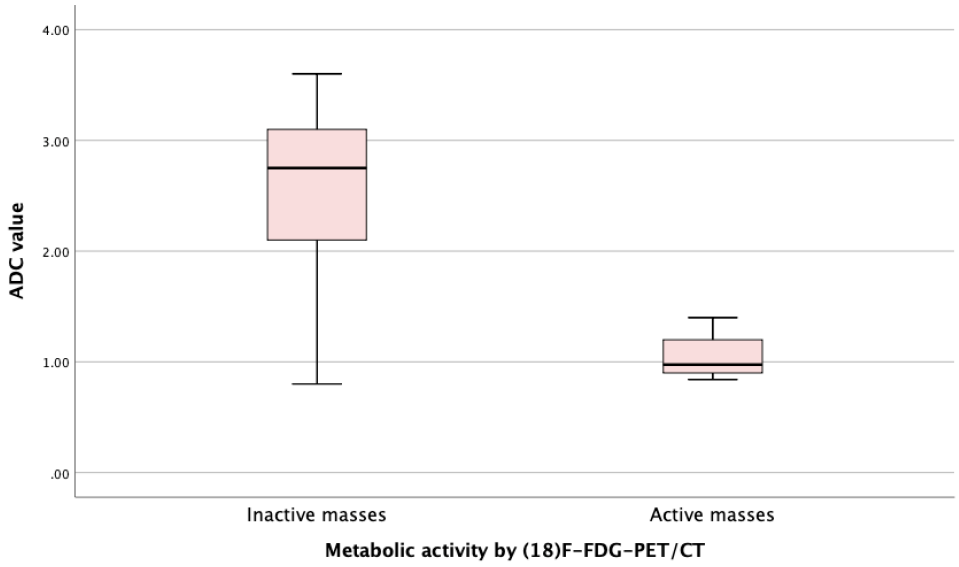
Positron emission tomography-computed tomography (PET/CT) was also performed for the aforementioned patients showing hypermetabolism in 41,7% (n=10) of the masses and no metabolic changes in the remaining 58,3% (n=14).

There was no statistically significant difference in mean attenuation measured on CT between metabolically active and inactive masses (p=0,546). There was a statistically significant difference in apparent diffusion coefficient between metabolically active and inactive masses (p=0,005).

DISCUSSION

Masses of the posterior mediastinum are usually found incidentally during routine chest investigations, and in most of the cases, they appear as rounded, sharply marginated lesions [1, 2]. In this study, we found that the majority of the posterior paravertebral masses 66,7% (n=16) presented with a well-defined circumscribed border, and remaining cases showed sharply marginated ill-defined borders. These

Fig 8. The difference between ADC value by metabolic activity



findings were not specific, so more precise imaging modalities were used.

We predicted that the nature of the mass could be distinguished by using a CT or MRI scan.

On CT, they can have both low and high attenuation, depending on cystic content [2]. Intrathoracic meningoceles and cystlike lesions have low attenuation [2, 20]. Bronchogenic cysts, lymphangiomas can have both low and high attenuation [2, 5]. Fluid, soft tissue, fat or calcium may be apparent in the case of mature cystic teratoma [8]. Cystlike lesions may have a complex structure with a fluid like areas [20]. As a result, imaging findings are similar in some types of paravertebral masses, so only the attenuation, structure, content and relation with other structures can be assessed. In the present study, CT images showed that the majority of cystic masses 79,2% (n=19) had heterogeneous structure, 33,3% (n=8) showed no enhancement and the remaining masses showed a various degree of enhancement with no significant difference of mean attenuation between the two, showing similarities to a study by K. Pulasani et al. that displayed heterogeneous enhancement in the majority (44%) of the tumours, no enhancement in 28% of the masses and no significant differences between structural characteristics and malignancy [30]. However, relying just on these findings, we cannot conclude in determining whether the mass is malignant or benign.

Correspondingly to a study by Chandna P et al. that showed 64% of oesophagal tumours were homogenous on CT scan, in our study the majority 77,2% (n=44) of oesophagal masses also had homogenous structure, however, after the administration of intravenous contrast medium 52,6% (n=30) showed nonhomogeneous enhancement [27]. When comparing malignant oesophagal tumours, there was a statistically significant difference between attenuation before and after the administration of intravenous contrast medium ($p<0,001$) similarly to a study by Abbey J. Winant et al. [28].

MRI can help to confirm the cystic nature of the mass [6]. This imaging modality is beneficial for long-term follow-ups, as well [17]. The diagnosis of a benign or malignant process can be made by calculating the mean apparent diffusion coefficient (ADC) value [22]. Tondo et al. reported that the sensitivity of this technique is 90% and specificity - 100% [22]. In our study, we found a statistically significant difference of apparent diffusion coefficient between metabolically active masses 1,05 0,06 x 10-3mm2/s and inactive masses 2,45 0,24 x 10-3mm2/s ($p=0,005$), equivalently to a study by Shin K.E. that got the same results with mean averages of 1.46 ± 0.50 x 10-3mm2/s and 3.67 ± 0.87 x 10-3mm2/s respectively [29].

CONCLUSIONS

A wide range of diagnostic methods can be used to diagnose paravertebral mediastinal pathologies. In our study, we concluded that conventional chest radiography could be helpful to define the anatomical location, borders and size of the masses. Multislice computed tomography can help to obtain information about densities and CE of the lesion. In MRI different sequences, the masses have an isointense or hyperintense signal which provides more information about the inner structure of lesion. Apparent diffusion coefficient (ADC) in MRI can be helpful distinguishing malignant from benign masses.

REFERENCES

1. Osama Saber Eldib, Abdelmeged Salem. Surgical management of mediastinal cysts, Journal of the Egyptian Society of Cardio-Thoracic Surgery, Volume 24, Issue 1, 2016. https://doi.org/10.1016/j.jescts.2016.03.001

2. Mi-Young Jeung, Bernard Gasser, Afshin Gangi, et al. Imaging of Cystic Masses of the Mediastinum. RadioGraphics 2002 22:suppl_1, S79-S93 https://pubs.rsna.org/doi/10.1148/radiographics.22.suppl_1.g02oc09s79

3. Juanpere, S., Cañete, N., Ortuño, P. et al. A diagnostic approach to the mediastinal masses. Insights Imaging 4, 29–52 (2013). https://doi.org/10.1007/s13244-012-0201-0

4. Takahashi K, et al. Computed tomography and magnetic resonance imaging of mediastinal tumors. J Magn Reson Imaging. 2010;32:1325–1339. doi: 10.1002/jmri.22377.

5. McAdams HP, Kirejczyk WM, Rosado-de-Christenson ML, et al. Bronchogenic cyst: imaging features with clinical and histopathologic correlation. Radiology. 2000;217:441-6.

6. Lyon RD, McAdams HP. Mediastinal bronchogenic cyst: demonstration of a fluid-fluid level at MR imaging. Radiology 1993; 186:427-428.

7. Moeller KH, Rosado-de-Christenson ML, Templeton PA. Mediastinal mature teratoma: imaging features. AJR Am J Roentgenol 1997; 169:985-990.

8. Tecce PM, Fishman EK, Kuhlman JE. CT evaluation of the anterior mediastinum: spectrum of disease. RadioGraphics 1994; 14:973-990.

9. Brown LR, Aughenbaugh GL. Masses of the anterior mediastinum: CT and MRI findings. AJR Am J Roentgenol 1991; 157:1171-1180.

10. Gocer AI, Tuna M, Gezercan Y et al. Multiple anterolateral cervical meningoceles associated with neurofibromatosis, Neurosurg Rev, 1999, vol. 22 (2–3)(pg. 124-126)

11. Mehmet Turgut, Cumhur Alhan, Mutlu Cihangiroglu, Mehmet Sah Topcuoglu, Isolated giant intrathoracic meningocele associated with vertebral corpus deformity, Interactive CardioVascular and Thoracic Surgery, Volume 3, Issue 2, June 2004, Pages 381–383, https://doi.org/10.1016/j.icvts.2004.02.009

12. Vilela, Tiago Tavares, Daher, Renato Tavares, Nóbrega, Mariana Domiciano Albuquerque, Ximenes Filho, Carlos Alberto, Montandon, Cristiano, & Montandon Júnior, Marcelo Eustáquio. (2009). Congenital mediastinal cysts: imaging findings. Radiologia Brasileira, 42(1), 57-62. https://doi.org/10.1590/S0100-39842009000100012

13. Charruau L, et al. Mediastinal lymphangioma in adults: CT and MRI imaging features. Eur Radiol. 2000;10:1310–1314. doi: 10.1007/s003300000380.

14. Ödev K, Arıbaş BK, Nayman A, Arıbaş OK, Altınok T, Küçükapan A. Imaging of cystic and cystlike lesions of the mediastinum with pathologic correlation. J Clin Imaging Sci 2012; 2: 33.

15. Shaffer K, Rosado-de-Christenson ML, Patz EF, Jr, Young S, Farver CF. Thoracic lymphangioma in adults: CT and MR imaging features. AJR Am J Roentgenol. 1994;162:283–9.

16. Savage J, Casey J, McNeill I, et al. Neurenteric cysts of the spine. J Craniovertebr Junction Spine. 2010;1(1):58.

17. Brooks BS, Duvall ER, el Gammal T, Garcia JH, Gupta KL, Kapila A. Neuroimaging features of neurenteric cysts: Analysis of

nine cases and review of the literature. AJNR Am J Neuroradiol. 1993;14:735–46.

18. Menezes AH, Traynelis VC. Spinal neurenteric cysts in the magnetic resonance imaging era. Neurosurgery. 2006;58:97–105. discussion 97-105.

19. Youssriah Yahia Sabri, Mona Ahmed Fouad, Hebata-Allah Hany Assal, Hassan Ebrahim Abdullah. Cystic lesions in multi-slice computed tomography of the chest: A diagnostic approach. The Egyptian Journal of Radiology and Nuclear. Medicine, Volume 47, Issue 4, 2016.

20. K.D. Hopper, L.F. Diehl, M.A. Cole, J.C. Lynch, J.W. Meilstrup, M.A. McCauslin. The significance of necrotic mediastinal lymph nodes on CT in patients with newly diagnosed Hodgkin disease. Am J Roentgenol, 155 (6) (1990), pp. 267-270

21. Razek AA. Diffusion magnetic resonance imaging of chest tumors. Cancer Imaging. 2012;12(3):452–463. Published 2012 Oct 26. doi:10.1102/1470-7330.2012.0041

22. Tondo F, Saponaro A, Stecco A, et al. Role of diffusion-weighted imaging in the differential diagnosis of benign and malignant lesions of the chest–mediastinum. Radiol Med. 2011;116:720–733. doi: 10.1007/s11547-011-0629-1. . PMid:21293944.

23. Satoh S, Kitazume Y, Ohdama S, Kimula Y, Taura S, Endo Y. Can malignant and benign pulmonary nodules be differentiated with diffusion-weighted MRI? Am J Roentgenol. 2008;191:464–470. doi: 10.2214/AJR.07.3133.

24. van Vliet EPM, Heijenbrok-Kal MH, Hunink MGM, Kuipers EJ, Siersema PD. Staging investigations for oesophageal cancer: a meta-analysis. Br J Cancer2008;98:547-57.doi:10.1038/sj.bjc.6604200 pmid:18212745

25. van Rossum PS, van Hillegersberg R, Lever FM, et al. Imaging strategies in the management of oesophageal cancer: what's the role of MRI? Eur Radiol. 2013;23:1753–1765.

26. Rosado-de-Christenson ML, Templeton PA, Moran CA. From the archives of the AFIP. Mediastinal germ cell tumors: radiologic and pathologic correlation. RadioGraphics 1992; 12:1013-1030.

27. Chandna P, Siddesh MB, Jeevika MU, Kochar PKT. CT imaging and staging of carcinoma oesophagus. Int J Res Med Sci 2017;5:2021-9.

28. Abbey J. Winant, Marc J. Gollub, Jinru Shia, Christina Antonescu, Manjit S. Bains, and Marc S. Imaging and Clinicopathologic Features of Esophageal Gastrointestinal Stromal Tumors. Levine American Journal of Roentgenology 2014 203:2, 306-314

29. Shin, K.E., Yi, C.A., Kim, T.S. et al. Diffusion-weighted MRI for distinguishing non-neoplastic cysts from solid masses in the mediastinum: problem-solving in mediastinal masses of indeterminate internal characteristics on CT. Eur Radiol 24, 677–684 (2014). https://doi.org/10.1007/s00330-013-3054-0

30. Kireet Pulasani , Indira Narayanaswamy , H V Ramprakash. Evaluation of Mediastinal Mass Lesions Using Multi-detector Row Computed Tomography and Correlation with Histopathological Diagnosis. International Journal of Scientifi c Study. Volume 3, Issue 6, Sep 2015.

Angioplasty of v. mesenterica sup. Occlusion: clinical case report

Domas Bajerūnas[1], Kotryna Mockaitytė[1], Andrius Pranculis[2]

[1] Lithuanian University of Health Sciences, Academy of Medicine, Faculty of Medicine, Kaunas,Lithuania
[2] Hospital of Lithuanian University of Health Sciences Kauno Klinikos, Department of Interventional Radiology, Kaunas, Lithuania

ABSTRACT
Cases of symptomatic v. mesenterica sup. (VMS) occlusion is rare. Patients usually complain of abdominal pain and present gastrointestinal bleeding. Occlusion can cause v. portae thrombosis and even lead to congestive bowel infarction [1,2]. We present a case of 49-year-old man, who complained about recurrent gastrointestinal bleeding throughout the period of two years and was finally treated with revascularisation of VMS at the Hospital of Lithuanian University of Health Sciences (HLUHS) Kauno klinikos.

Keywords: V. mesenterica sup. Angioplasty, v. mesenterica sup. Occlusion.

INTRODUCTION

V. mesenterica superior (VMS) collects blood from the jejunum, ileum and, when it joins with the v. splenica, forms v. portae. Impaired blood drainage occurs due to mesenteric venous hypertension, then patients complain of abdominal pain and bleeding from the lower gastrointestinal tract. Also varicose veins in the small intestine could be observed [1]. Symptomatic VMS occlusion is rare and endovascular treatment is complicated and very limited [1,3,4]. With the progression of critical stenosis, v. portae thrombosis and bowel infarction may occur [1,2]. Non-malignant causes of occlusions are pancreatitis, surgical interventions and abdominal trauma. Malignant causes usually are pancreatic adenocarcinoma and other abdominal tumours [2].
Occlusion can be visualised by performing indirect angiography of the portal system by contrasting arteries or magnetic resonance angiography, but these techniques are used less frequently [5]. When it comes to diagnosing this disease, computer tomography with intravenous contrast is the modality of choice. Direct angiography is only possible by transjugular route or through v. portae percutaneous puncture, but this is only for diagnostic purposes prior to treatment. Patients with progressing symptoms may be treated with VMS revascularisation. In such cases, implantation of a balloon expandable stent is a minimally invasive alternative to open surgery [5].
We report a 49-year-old man who was treated throughout the period of 2 years for recurrent gastrointestinal bleeding. For the scarcity of information, our purpose is to improve medical staff knowledge of VMS occlusion examination and treatment.

CASE DESCRIPTION

In 2011 a 49-year-old male underwent pancreatoduodenal resection due to abdominal trauma. Later he was operated again due to anastomosis stricture. In January 2016, the patient was hospitalised to HLUHS Kauno klinikos Surgery department because he began to complain of gastrointestinal bleeding. EGD was performed and varicose veins were found at the gastrointestinal junction. After two weeks laparotomy was performed with adhesiotomy and anastomosis reconstruction. After 6 months gastrointestinal bleeding occurred again. Selective a. mesenterica sup. Et inf. And truncus coeliacus angiography was performed - no extravasation was found. After one month, on the 2th August 2016, the patient underwent fibrocolonoscopy, large intestine to the ileum terminale was examined. Dark coloured contents, blood clots with fresh blood admixture were visible throughout the large in-

testine, but during a more detailed examination bleeding sites could not be determined. On the same day a. mesenterica sup. Et inf. and truncus celiacus angiography was performed, but no extravasation was noticed. It was decided to perform a. lienalis embolisation due to a possible fistula in the colon. 3 days after, the patient again had gastrointestinal bleeding and urgent angiography was performed, but no extravasation was seen, only a distal a. gastroduodenalis filling from a. mesenterica inf. Was noticed and a denser network of small arteries in the lienal corner of the colon. The area was embolised with two coils. There was no recurrence of bleeding after the procedure. Bleeding occurred again after a month, and the patient was treated conservatively.

On 18th February 2017 patient again had gastrointestinal bleeding, but intestinoscopy showed no results. A day after, an abdominal CT with arteriography was performed, which found that VMS does not differentiate, no clear filling defects in v. portae and v. lienalis were found.

A year later, on 13th February 2018, an abdominal CTA was performed in which a potentially thrombotic VMS was found (Fig. 1). On the 10th April 2018, the patient was discussed in a multidisciplinary consilium for further treatment tactics: it was decided to revascularize VMS. The patient was hospitalised on 14th of April 2018; his condition was satisfactory. On the 17th April 2018, VMS occlusion was recanalised through a percutaneous transhepatic route using Boston scientific "Mustang" 5x40 mm and 8x40 mm balloon catheters and Alvimedica CID "Isthmus" 9x19 mm carbon-coated stent (Fig. 2). For postoperative care analgesics and fraxiparine 0.6 ml were administered. After two days, fraxiparine was discontinued, clopidogrel was prescribed after VMS stenting gastrointestinal bleeding did not reoccur.

Fig. 1. CT angiography 13th February 2018 distal part occlusion of v. mesenterica sup.

Fig. 2. V. mesenterica sup. Angiography. 17th April 2018 after v. mesenterica sup. Stenting. Blood flow was restored to the distal part of the vessel.

DISCUSSION

Mesenteric venous thrombosis 95 % of the cases involves VMS, and only 5 % of the cases involve v. mesenterica inferior because the distal part of the colon has a good collateral system [6]. In an acute situation, there would be insufficient time to develop collateral circulation, and a symptomatic VMS thrombosis may result in a transmural bowel infarction [5].

According to Singal et al., chronic VMS is typically found accidentally in cirrhotic patients during CT imaging with evidence of sequelae of portal hypertension, such as gastrointestinal varicose veins and splenomegaly [5]. In our case, the patient did not have chronic liver disease, but he had undergone pancreatoduodenal resection in 2011, which could have led to VMS occlusion. The main symptom was reoccurring gastrointes-

tinal bleeding which lasted for nearly two years. Other researchers like Russell et al. and Lennard et al., presented case reports in which patients presented symptoms of epigastric pain, nausea and vomiting [7,8]. The main difference was that both patients had acute VMS thrombosis oppose to our chronic case and therefore showed different disease signs.

In the current literature, we can find many v. portae stenting examples. Usually, these are the cases of portal vein obstruction due to malignant masses and anastomotic stenosis after liver transplantation [9–11]. In the case of VMS thrombosis, it is treated with thrombolysis, thrombectomy, resection and anastomosis or transjugular intrahepatic portosystemic shunt [5,12].

Only a few clinical cases and one peer-reviewed study describe VMS stenting confirming technical success and clinical effectiveness [3,5,13]. Hellman et al. described seven VMS stenting cases with carcinomas of the abdominal cavity resulting in small bowel venous stasis. For treatment, a 10x60 mm Luminex stent was used. For five patients, symptoms have resided; for the other two, the symptoms persisted [1]. Our patient was stented transjugular using a balloon-expandable stent. Stent diameter was selected accordingly to v.portae and VMS. Thickness. The radius of these vessels is rarely less than 1 cm. Other authors also recommend the use of a stent of at least 10 mm in diameter to prevent acute occlusion after the procedure [13]. In our case, a 9 mm stent was used, no complications were observed after the procedure.

CONCLUSIONS

VMS occlusion is a rare medical disease. Due to the lack of clinical cases and articles, there are currently no precise guidelines for endovascular treatment. Based on analysed articles and our own experience we can say that VMS stenting is a minimally invasive and clinically effective alternative to open surgery.

REFERENCES

1. Hellman P, Hessman O, Åkerström G, Stålberg P, Hennings J, Björck M, et al. Stenting of the superior mesenteric vein in midgut carcinoid disease with large mesenteric masses. World J Surg. 2010;34(6):1373–9.

2. Woodrum DA, Bjarnason H, Andrews JC. Portal Vein Venoplasty and Stent Placement in the Nontransplant Population. J Vasc Interv Radiol. 2009;20(5):593–9.

3. Mauri G, Monti L, Pedicini V. Interventional management of in-stent thrombosis after superior mesenteric vein stenting. EJVES Extra. 2011;22(3):231–239.

4. Zhang WG, Liu DM, Li Z, Wang YL, Ding PX, Zhou PL, et al. Endovascular treatment for extrahepatic portal vein bifurcation stenosis after a whipple procedure using the kissing stents technique. Ann Vasc Surg. 2014;28(1):264.e13-264.e16.

5. Singal AK, Kamath PS, Tefferi A. Mesenteric venous thrombosis. Mayo Clin Proc. 2013;88(3):285–94.

6. Harnik IG, Brandt LJ. Mesenteric venous thrombosis. Vasc Med. 2010;15:407–418.

7. Russell CE, Wadhera RK, Piazza G. Mesenteric venous thrombosis. Circulation. 2015;131(18):1599–603.

8. Lee LYW, Aubrey-Jones H, Lacey R, De Silva A. Mesenteric vein thrombosis; not going with the flow. Vol. 16, BMJ Case Reports. 2014. p. 206–10.

9. Wei BJ, Zhai RY, Wang JF, Dai DK, Yu P. Percutaneous portal venoplasty and stenting for anastomotic stenosis after liver transplantation. World J Gastroenterol. 2009;15(15):1880–5.

10. Yang J, Xu MQ, Yan LN, Lu WS, Li X, Shi ZR, et al. Management of venous stenosis in living donor liver transplant recipients. World J Gastroenterol. 2009;15(39):4969–73.

11. Sakurai K, Amano R, Yamamoto A, Nishida N, Matsutani S, Hirata K, et al. Portal vein stenting to treat portal vein stenosis in a patient with malignant tumor and gastrointestinal bleeding. Int Surg. 2014;99(1):91–5.

12. Hmoud B, Singal AK, Kamath PS. Mesenteric Venous Thrombosis. J Clin Exp Hepatol. 2014;4(3):257–63.

13. Beyer LP, Wohlgemuth WA, Uller W, Pregler B, Goessmann H, Niessen C, et al. Percutaneous treatment of symptomatic superior mesenteric vein stenosis using self-expanding nitinol stents. Eur J Radiol. 2015;84(10):1964–9.

Alveolar echinococcosis: clinical case presentation

Gabija Bagužytė[1], Paulina Tekoriutė[1], Diana Barkauskienė[2]

[1]*Lithuanian University of Health Sciences, Academy of Medicine, Faculty of Medicine, Kaunas, Lithuania*
[2]*Department of Pulmonology, Lithuanian University of Health Sciences, Kaunas, Lithuania*

ABSTRACT
Echinococcosis is a parasitic disease caused by Echinococcus species. Tapeworm Echinococcus multilocularis causes alveolar echinococcosis (AE) which is a significant worldwide public health problem with potential life-threatening outcomes. We present a case report of advanced AE with lesions in liver and dissemination to vena cava inferior and lungs.

Keywords: echinococcus multilocularis, Alveolar echinococcosis, Malignant parasite, Mimicking cancer.

INTRODUCTION

Echinococcosis is a zoonosis caused by a tapeworm species belonging to the genus Echinococcus, family Taeniidae (1, 2). In humans, E. granulosus occurs as cystic echinococcosis, E. multilocularis causes alveolar echinococcosis (AE), and E. vogeli and E. oligarthrus as polycystic echinococcosis (3). E. multilocularis tapeworm is endemic in many regions of the world, but parts of the Northern hemisphere, such as North America, China, central and eastern Europe and the Baltic states, are the most concerning (4, 5, 6). In Lithuania alone between 1997 and 2013, a total of 179 AE cases have been reported (7). Diagnosing this disease is complicated due to extended incubation time, various clinical manifestations and mimicking of differential diagnoses (8). We report a case of advanced AE, which is a rare infection and may even have fatal consequences. Our purpose is to raise awareness of diagnosing this condition among various physicians.

CASE REPORT

A 59-year-old woman referred by a general practitioner to the pulmonology department presented to our hospital with complaints of coughing up phlegm and blood, and weight loss.
During a preventative health examination, a front chest X-ray was performed, and it revealed diffuse 13-17 mm diameter high-density formations on both sides in the lungs. The patient was referred to a pulmonologist for a further examination suspecting a malignant process.
Second X-ray scan was performed showing multiple high-density various sizes with the largest measuring approximately 15 mm mass lesions with clear boundaries, mostly in the periphery of the lungs (Figure – 1). Radiological findings are to be differentiated with primary cancer and metastasis.
The patient claimed to be allergic to iodine and therefore, was hospitalized for computed tomography (CT) scan. On the day of admission, her vitals were normal, vesicular breathing and no crackles were present. A consensus was made to perform a CT scan for suspected lung tumour and spreading during a pulmonologists Concilium. The patient was treated with dexamethasone and clemastine according to the protocol against iodine allergy.
Contrast-enhanced chest and abdominal CT revealed multiple polisegmental heterogenic-density various size mass lesions with a policycle outline situated along the vessels mostly in the periphery of both lungs, some with mild enhancement. The most prominent lesion is measuring approximately 16 x 11 mm in the right first lung segment (Figure – 2, 3). CT also showed a heterogenic mild enhancement lesion with a policycle outline, cystic components and calci-

fications measuring approximately 12 x 82 x 78 mm, in the left lobe of the liver (Figure - 4). Vena cava inferior (up to right atrium level) and the vault of the diaphragm were also infiltrated.

A few merging similar structures pathologic nodes measuring approximately 28 x 15 mm and nodules situated along the oesophagus with the largest measuring approximately 12 x 12 mm were present between the left lobe of the liver and the lesser curvature of stomach within the left heart ventricle. With these findings, hepatic echinococcosis with invading to vena cava inferior and hematogenous lung dissemination were suspected radiologically.

Initial laboratory tests showed haemoglobin level 147 g/l, white blood cells count 12,3 x 109/l, eosinophils 0,0 x 109/l, platelet count 268 x 109/l. C – reactive protein, creatinine, urea, alanine and aspartate aminotransferase, and electrolytes were normal. In addition, the patient was positive for the presence of IgG antibodies against Echinococcus spp. 74,2 g/l.

Based on the clinical symptoms, imaging examinations, and serology test, Echinococcus multilocularis infection was diagnosed. Albendazole treatment in 400 mg two daily doses was started, and the patient was referred to an infectologist for an immediate consultation.

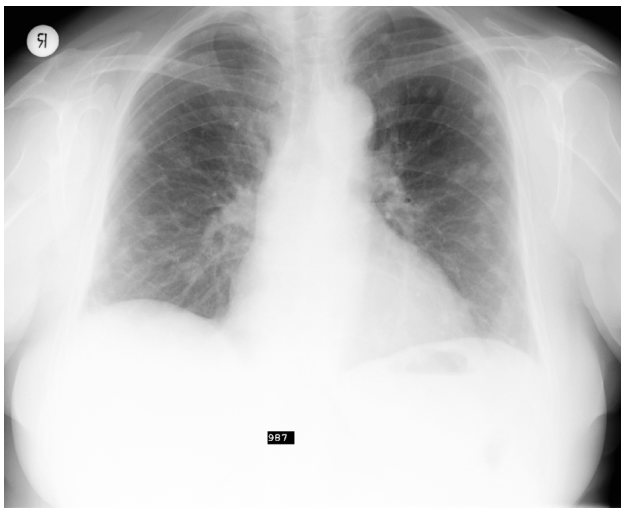


Figure 1. Plain chest X-ray – multiple various size mass lesions in the periphery of both lungs

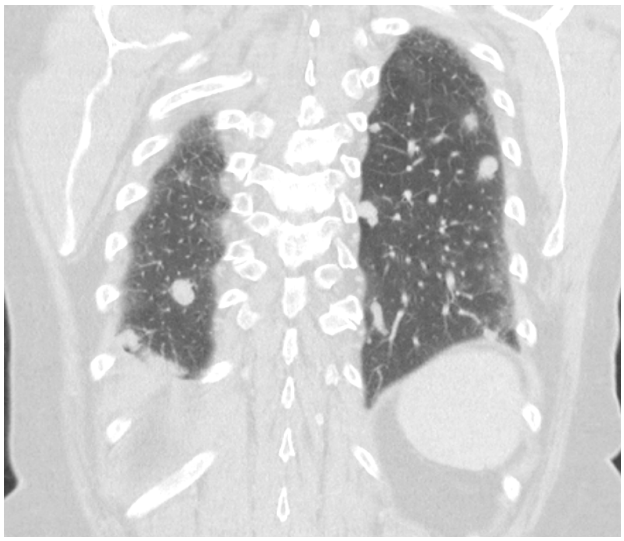


Figure 2. Chest CT, coronal view - multiple polisegmental heterogenic-density mass lesions situated along the vessels mostly in the periphery of both lungs.

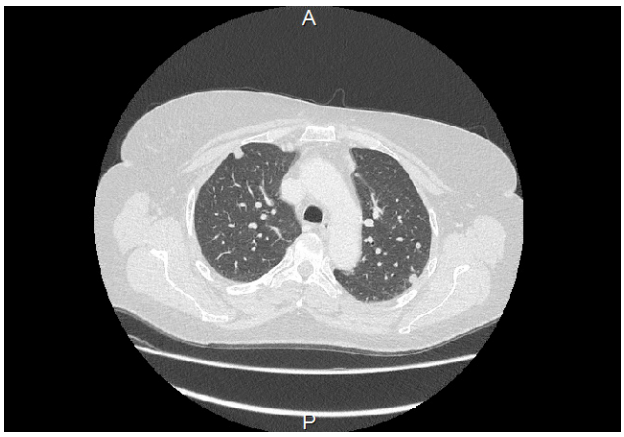


Figure 3. Chest CT, axial view - multiple mass lesions with a policycle outline mostly in the periphery of both lungs.

Figure 4. Thoraco-abdominal CT, coronal view - a heterogenic mild enhancement lesion, cystic components and calcifications in the left lobe of the liver

DISCUSSION

AE caused by E. multilocularis tapeworm is a worldwide endemic concern. (4). Over the past few decades in Europe emergence of AE in humans was reported in France (509; diagnosed between 1982 and 2011), Switzerland (494; 1956-2005), Lithuania (179; 1997-2013), Germany (114; 2003-2013), Poland (121; 1990-2011), Latvia (43; 1996-2010) Slovakia (26; 2000-2013) and Czech Republic (20; 1998-2014) (7, 9, 10). Moreover, countries previously documented to be free from E. multilocularis infection, including, the UK, Ireland, Malta, Norway and Finland take actions to measure the risk of introducing this parasite into their areas through imported pets and wildlife animals (5).

The definite hosts are wild carnivores – mainly red fox, whereas rodents are intermediate hosts in the life cycle of E. multilocularis (2, 3). Cats and domestic dogs may be involved in a synanthropic cycle of adult tapeworms (2). The eggs with oncospheres produced by the adult parasite living in the small intestine of the definitive hosts are released into the environment with faeces, and the cycle continues with the digestion of contaminated food by the intermediate host (2, 3). Humans are accidental dead-end hosts acquiring the infection through the faecal-oral route (10).

AE is a chronically progressive infection with a high degree of disability, morbidity and mortality in the absence of curative surgery and anti-helminthic treatment (4, 8, 11). The incubation period may take 5 to 15 years without any significant symptoms leading detection by chance or during screening programmes (12). Our patient was also referred to as seek a pulmonologist for further inspection because of suspected metastatic lung lesions after a screening programme.

Hepatic invasion is the most frequent occurrence of echinococcosis followed by the lungs, but it is rare in other organs (3, 13). The primary clinical signs depend on the organ involved and the degree of the invasion and are usually nonspecific epigastric pain and jaundice, high fever, coughing, but malaise, dizziness, headache and weight loss, can also develop (3, 14, 15).

Hepatic AE complications include biliary obstruction, cholangitis and sepsis (11, 14). Further damage of liver parenchyma can cause obstruction of vessels leading to vascular occlusion/thrombosis of the portal veins with portal hypertension of the hepatic veins, and the Budd–Chiari syndrome, and of the vena cava and the right atrium (14).

Although AE is benign, it presents a cancer-like appearance in the liver with destructive tissue growth and metastatic spread in lymph nodes, lung, brain, bone, spleen and other organs through blood vessels and lymphatic vessels (13, 14, 15, 16). Finally, in the advanced stages, a bacterial liver abscess may be mimicked by superinfection of central necrotic cavities (17) which makes the diagnostics even more complicated.

Diagnosis of AE is based on the following aspects: clinical findings and epidemiological data, imaging studies, and histopathology, and serology (11, 12).

Gathering information about patient's history, living space and contact of farm animals that is the source of infection, clinical symptoms such as abdominal pain or discomfort, a mass/masses in hepatic region, jaundice, high fever or dizziness, headache, coughing (15) is the first step when suspecting echinococcosis.

Imaging studies for AE include ultrasonography (USG), CT and magnetic resonance imaging (MRI) (13). USG is useful for a screening diagnosis as it shows firm echo lesions with heterogeneous echoes inside when examining the liver (13, 15). No envelope is present around the lesion of hepatic AE, and the margin is irregular so it can be misdiagnosed as primary liver cancer, hepatic hemangioma and focal hyperplasia (15). For further examination after USG, CT and MRI are used (13). CT imaging shows an inhomogeneous solid mass, unclear boundary and no noticeable enhancement in the enhanced scan so lesions may be vesicles, calcification, and liquefaction necrosis. In contrast, on contrast-enhanced CT, the periphery of the mass may be enhanced, and multicentric vesicles may be visible (15). MRI supports the diagnosis by showing multi-vesicular morphology with a clear boundary after enhancement. (13, 15).

The most critical imaging feature of AE is calcification. There should be clusters of microcalcifi-

cations or plaque-like calcific foci with an irregular distribution in any part of the lesion (13).
During a histopathologic examination of E. multilocularis the parasitic vesicles have a Periodic-Acid-Schiff (PAS)+ laminated layer. Epithelioid cells, macrophages, fibroblasts, giant multinucleated cells and various cells of nonspecific immune response, usually surrounded by lymphocytes are the composition of periparasitic granuloma (1).
The antigen detection assay with a high diagnostic sensitivity of 90–100% and a specificity of 95–100% is helpful when diagnosing AE (1, 13).
The principles of treating AE are to stop the invasion of the lesion into surrounding organs and to prevent dissemination (13). Radical surgical resection followed by benzimidazoles as anti-infective drugs for two years to avoid recurrence is the first-choice treatment, taking into account the patient-specific stage of the disease. (12, 13, 18, 19). Unfortunately, in advanced AE stages, radical surgery is not feasible (20). Our patient had E. multilocularis infiltrations in vena cava inferior, making radical surgery hazardous due to the risks of air embolism or uncontrolled hemorrhage (21).
Inoperable patients must undergo long-term treatment with benzimidazoles, mostly albendazole (ABZ) or alternatively mebendazole (MBZ) when ABZ is not tolerated (18, 21, 22). Recommended dosages of ABZ are 10–15 mg/kg/day, in 2 doses, recommended with a high-fat meal to ensure absorption (18, 20). Alternatively, MBZ is given at a dose of 40–50 mg/kg/day, divided into three doses (20).
All in all, the most crucial factor in improving prognosis of AE is supposed to be early diagnosis following with complete resection (19).

CONCLUSION

Our case report is a reminder for doctors that echinococcosis may present as cancer-like lesions both in clinical manifestation and radiological imaging. It is noteworthy to involve this zoonosis in the differential diagnosis when suspecting cancer and metastases in various organs.

REFERENCES

1. Brunetti E, Kern P, Vuitton DA. Expert consensus for the diagnosis and treatment of cystic and alveolar echinococcosis in humans. Acta Tropica 2010;114(1):1-16.

2. Dybicz M, Borkowski PK, Padzik M, Baltaza W, Chomicz L. Molecular determination of suspected alveolar echinococcosis requiring surgical treatment in human cases from Poland. Annals of parasitology 2018;64(4):339-342.

3. Bulakçı M, Kartal MG, Yılmaz S, Yılmaz E, Yılmaz R, Şahin D, et al. Multimodality imaging in diagnosis and management of alveolar echinococcosis: an update. Diagnostic and interventional radiology (Ankara, Turkey) 2016 May;22(3):247-256.

4. Shen H, Chen K, Li B, Zhang H, Yang K, Chen Y, et al. Two-stage hepatectomy for multiple giant alveolar echinococcosis. Medicine 2017 August;96(33):e7819.

5. Gottstein B, Stojkovic M, Vuitton DA, Millon L, Marcinkute A, Deplazes P. Threat of alveolar echinococcosis to public health – a challenge for Europe. Trends in Parasitology 2015;31(9):407-412.

6. Dušek D, Vince A, Kurelac I, Papić N, Višković K, Deplazes P, et al. Human Alveolar Echinococcosis, Croatia. Emerging Infect Dis 2020 Feb;26(2):364-366.

7. Marcinkutė A, Šarkūnas M, Moks E, Saarma U, Jokelainen P, Bagrade G, et al. Echinococcus infections in the Baltic region. Veterinary Parasitology 2015 Oct 30,;213(3-4):121-131.

8. Meinel TR, Gottstein B, Geib V, Keel MJ, Biral R, Mohaupt M, et al. Vertebral alveolar echinococcosis—a case report, systematic analysis, and review of the literature. The Lancet Infectious Diseases 2018 /03/01;18(3):e87-e98.

9. Gawor J. Alveolar echinococcosis in Europe and Poland. Threats to humans. Przeglad epidemiologiczny 2016;70(2):281.

10. Cambier A, Leonard P, Losson B, Giot J, Bletard N, Meunier P, et al. Alveolar echinococcosis in southern Belgium: retrospective experience of a tertiary center. Eur J Clin Microbiol Infect Dis 2018 Jun;37(6):1195-1196.

11. Caire Nail L, Rodríguez Reimundes E, Weibel Galluzzo C, Lebowitz D, Ibrahim YL, Lobrinus JA, et al. Disseminated alveolar echinococcosis resembling metastatic malignancy: a case report. Journal of medical case reports 2017 Apr 18,;11(1):113.

12. Kern P. Clinical features and treatment of alveolar echinococcosis. Current Opinion in Infectious Diseases 2010 October;23(5):505–512.

13. Chu Z, Lv F, Zhu Z, Ouyang Y. Extrahepatic Primary Adrenal Alveolar Echinococcosis: A Review. Surgical Infections 2013 Aug 1,;14(4):418-421.

14. Gottstein B, Soboslay P, Ortona E, Wang J, Siracusano A, Vuitton DA. Chapter One - Immunology of Alveolar and Cystic Echinococcosis (AE and CE). In: Thompson RCA, Deplazes P, Lymbery AJ, editors. Advances in Parasitology: Academic Press; 2017. p. 1-54.

15. Yang J, Zhao Z, Li S, Chen H. A Case of Alveolar Echinococcosis Occurring in the Hilar Bile Duct. Korean J Parasitol 2019 -10;57(5):517-520.

16. Aydın Y, Ulaş AB, Topdağı Ö, Şener E, Öztürk G, Eroğlu A. Pulmonary metastasectomy with laparotomy in alveolar echinococcosis. Turk gogus kalp damar cerrahisi dergisi 2019 Oct;27(4):593-596.

17. Zheng X, Zou Y, Yin C. Rare presentation of multi-organ abdominal echinococcosis: report of a case and review of literature. International Journal of Clinical and Experimental Pathology 2015;8(9):11814.

18. Schmidberger J, Steinbach J, Schlingeloff P, Kratzer W, Grüner B. Surgery versus conservative drug therapy in alveolar echinococcosis patients in Germany – A health-related quality of life comparison. Food and Waterborne Parasitology 2019 September;16.

19. Qu B, Guo L, Sheng G, Yu F, Chen G, Wang Y, et al. Management of Advanced Hepatic Alveolar Echinococcosis: Report of 42 Cases. The American Journal of Tropical Medicine and Hygiene 2017 8 March;96(3):680.

20. Lundström-Stadelmann B, Rufener R, Ritler D, Zurbriggen R, Hemphill A. The importance of being parasiticidal… an update on drug development for the treatment of alveolar echinococcosis. Food and Waterborne Parasitology 2019 June;15.

21. Shen S, Kong J, Zhao J, Wang W. Outcomes of different surgical resection techniques for end-stage hepatic alveolar echinococcosis with inferior vena cava invasion. HPB (Oxford) 2019 09;21(9):1219-1229.

22. Siles-Lucas M, Casulli A, Cirilli R, Carmena D. Progress in the pharmacological treatment of human cystic and alveolar echinococcosis: Compounds and therapeutic targets. PLoS neglected tropical diseases 2018 Apr;12(4):e0006422.