DOI: https://doi.org/10.2298/SARH190312060L
UDC: 616.24-006-085

CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Metastatic atypical lung carcinoid treated with combined therapies

Nensi Lalić[1,2], Dragana Tegeltija[1,2], Ivan Kuhajda[1,2], Sanja Tomić[2], Ivica Lalić[3,2]

[1]Institute for Pulmonary Diseases of Vojvodina, Sremska Kamenica, Serbia;
[2]University of Novi Sad, Faculty of Medicine Novi Sad, Department of Nursing, Novi Sad, Serbia;
[3]Clinical Center of Vojvodina, Department of Orthopedic Surgery and Traumatology, Novi Sad, Serbia

SUMMARY

Introduction Lung carcinoids are considered a rare and uncommon group of lung tumors, making about 1% of all primary lung tumors. Atypical carcinoids are more aggressive than typical ones, with higher metastatic potential and worse prognosis and a 10-year survival rate of less than 60%.

Case outline In 2012, a 61-year-old male underwent the right lower lobectomy and the histopathological finding was an atypical lung carcinoid tumor. At the beginning of 2016, radiological and bronchoscopic progression of the disease was reported. Magnetic resonance imaging revealed enhanced nodular lesions compatible with liver metastases. The patient received endoluminal brachytherapy. Subsequently, the first line chemotherapy according to the cisplatin/etoposide (PE) protocol was applied. In August 2016, the somatostatin receptor scintigraphy (SRS) revealed secondary deposits with somatostatin receptor (SR) expression in the liver and lungs. The treatment with lanreotide injections was initiated. After five treatment courses, progression of the disease in the bronchial tree was verified and electro-cauterization and argon plasma cauterization of the tumor in the right main bronchus were performed. In September 2017, progression of the disease was verified again. The Oncology Board introduced the third line therapy with everolimus.

Conclusion The evidence supporting optimal treatment strategies for an atypical lung carcinoid tumor is lacking, but some recent publications indicate that multimodal treatment is associated with prolonged survival.

Keywords: lung; atypical carcinoid; somatostatin receptor; brachytherapy; everolimus

INTRODUCTION

Lung neuroendocrine tumors are classified into four categories, depending on their increasing biological aggressiveness: 1) typical carcinoid (TC), 2) atypical carcinoid (AC), 3) large-cell neuroendocrine cancer (LCNEC), and 4) small-cell lung cancer (SCLC). The guidelines for the Ki67 proliferation rate are given in the new WHO classification as the Ki67 index which amounts to 50–100% for SCLC, from 40–80% for LCNEC, 5–20% for AC, and falls below 5% for TC [1]. Lung carcinoids (LC) are rare pulmonary tumors making 1–5 % of all malignant lung tumors, having the incidence of 5–10/1,000,000 [2]. The standard treatment approach for lung carcinoid is a surgery, due to the fact these tumors are poorly sensitive to irradiation or chemotherapy [3].

TCs make up 70–90%, and ACs 10–30% of all LCs. The overall survival of patients undergoing total resection amounts to 92–100% for TCs, and 61–88% for totally resected AC. Inoperable LCs represent a considerable treatment challenge due to their poor chemo- and radiosensitivity. In addition, these tumors may reoccur or metastasize a decade after the primary resection [4, 5].

CASE REPORT

The approvals of the Committee on Ethics and of the Oncology Board were received for the purposes of this report.

A 54-year-old male with the symptoms of cough, fever, and dyspnea was admitted to the Institute for Pulmonary Diseases of Vojvodina in November 2012. The standard chest X-ray was presented with an oval opacity in the lower pole ow the right hilus (Figure 1). The chest computed tomography (CT) finding disclosed a tumorous lesion with the longest diameter of 6 cm, which infiltrated the S6 bronchus.

The endoscopy finding revealed a necrotic tumor emerging from the right Nelson bronchus, almost totally obstructing the basal bronchi. The histologic finding of the tumor biopsy sample correlated with lung adenocarcinoma. On November 12, 2012, the patient was submitted to lobectomy of the right lower lung lobe. The definite histopathology finding was tumor *carcinoides typus atypicus* (Figure 2). The TNM classification established the definite T2aN0M0 stage of the disease. Adjuvant chemotherapy was recommended, but the patient was not motivated for any additional treatment at that time. Regular postoperative Oncology Board controls were performed. All required analyses persisted normal for three years.

Received • Примљено: March 12, 2019
Accepted • Прихваћено: May 22, 2019
Online first: June 04, 2019

Correspondence to:
Nensi LALIĆ
University of Novi Sad
Faculty of Medicine
Department of Nursing
Hajduk Veljkova 3
21000 Novi Sad, Serbia
nensi.lalic@mf.uns.ac.rs

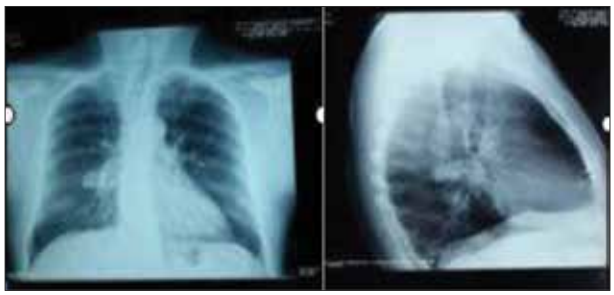

Figure 1. Chest X-ray finding: an oval opacity at the right hilus lower pole

inflammatory-type lesions at S2 on the right, accompanied with an intraluminal lesion of the intermediary bronchus. Unclearly demarcated liver lesions were also detected. The MRI finding from February 2016 was presented with multiple liver lesions characterized as secondary deposits. The whole-body positron emission tomography (PET) showed active nodes in the liver and an active lesion in the right lung (Figure 3).

Bronchoscopy performed in February 2016 revealed the following findings: tiny tumorous formations, smooth in the distal part of the trachea, and one larger smooth

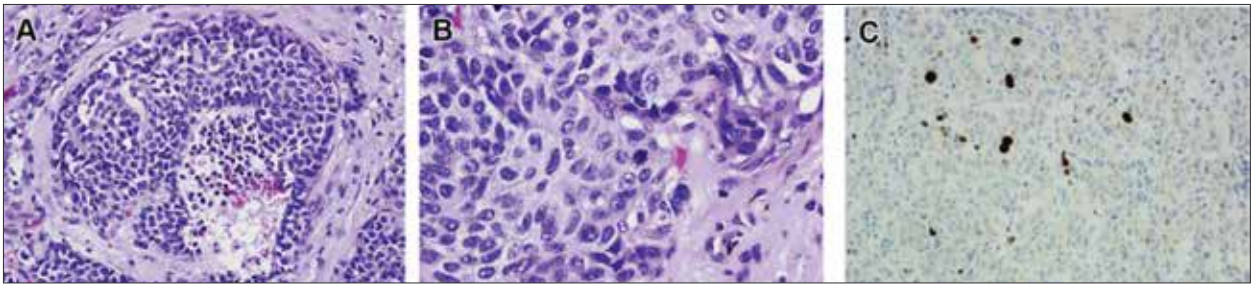

Figure 2. Atypical carcinoid: (A) punctate focus necrosis of carcinoid tumor cells and eosin; (B) a single mitosis in one tumor cell and cells with granular nuclear chromatin; (C) Ki-67 shows an intermediate proliferation rate

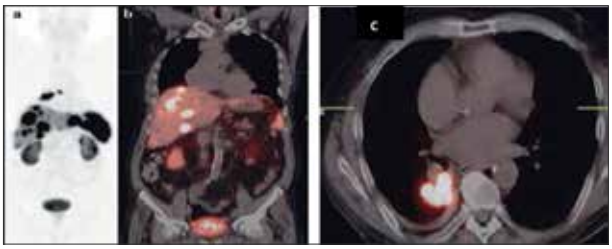

Figure 3. Magnetic resonance image of the abdomen: metastatic liver lesions, confirmed by positron emission tomography scan, which showed accumulation of radioactive fluorodeoxyglucose in the liver, as well as in the right lung

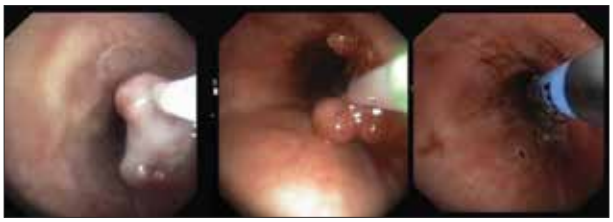

Figure 4. Endoscopic finding – the tumor removed applying the electrocautery loop; infiltrations in the tracheobronchial tree removed by argon plasm cauterization

On the regular control in November 2015, the patient had no symptoms, chest X-ray was identical to the former one, but CT of the abdomen revealed the liver involved by a few hypodense focal lesions in both lobes, probably hemangiomas. Erythrocyte pool liver scintigraphy was performed in December 2015 and detected no hemangioma-characteristic zones. The patient was scheduled for magnetic resonance imaging (MRI) of the abdomen. In January 2016, he developed fever and cough. The chest X-ray showed tiny inhomogeneous lesions in the right upper lung field and CT of the thorax disclosed infiltrative, tumor in the orifice of the upper bronchus on the right, entirely obstructing the orifices. The Oncology Board recommended endoluminal irradiation treatment, to be succeeded with chemotherapy (cisplatin/etoposide protocol). The patient completed this treatment in July 2016. On the control examination in August 2016, the finding on the lungs was in partial regression, but the finding on the liver persisted unchanged. All available histopathological samples were reassessed and they were AC of the lung, with low proliferative Ki index. The somatostatic receptor scintigraphy (SRS) was performed showing secondary deposits with SRS expression in the liver and lungs. The patient was started on lanreotide injections. After five therapy courses, progression of the disease in the tracheobronchial tree was verified. The tumor was removed by the electrocautery loop. Three months later, the tumor reoccurred at the same site so we reapplied the electrocautery loop, and then removed infiltrations in other localizations of the tracheobronchial tree by argon plasma cauterization (Figure 4). On the occasion of a new relapse episode in the right main bronchus when the lumen of the bronchus was reduced to 20%, spirometry and blood gas exchange findings persisted to be normal, but due to the latest endoscopy finding, interventional palliative bronchoscopy procedures (electrocautery of the tumor and argon plasma coagulation) were indicated.

In December 2017, the disease progression was registered in terms of an increased number and size of liver metastases, so the patient was selected for the third line treatment for AC with the everolimus drug. The patient was receiving this therapy from February to July 2018 when he developed undesirable side effects in terms of gastrointestinal symptoms and disease developed further liver progression resulting in the liver failure, so the drug

was discontinued in September 2018. At present, the patient has been receiving the symptomatic treatment with maximal supportive palliative oncological therapy.

DISCUSSION

LCs are included in the spectrum of neuroendocrine lung tumors, with a low frequency rate, ranging 0.2–2 per 100,000 inhabitants per year in the USA and Europe [6]. LCs belong to neuroendocrine lung tumors staged from the low-grade TC and intermediate-grade AC, to the high-grade LCNEC, and SCLC. TCs have less than 2 mitoses / 2 mm^2, and no necrosis, while ACs have 2–10 mitoses / 2 mm^2, and punctiform necrosis foci [7]. The diagnosis of LC is sometimes difficult to establish without immunohistochemical analyses (IHA) resulting in misdiagnosis, as it was the case in our patient, in whom the histopathological analysis of the tumor biopsy suggested lung adenocarcinoma and the definite diagnosis of carcinoid was at last established by IHA of surgically obtained biopsy samples and defined as atypical lung carcinoid. The reassessment procedure in our patient included the Ki67 proliferative index introduced in the clinical practice in 2015 by the new World Health Organization classification for neuroendocrine tumors, ranging 5–20% for ACs and amounting to < 5% for TCs. The Ki67 proliferative index in our patient's sample amounted to 15%, which additionally confirmed the IHA findings of AC [8].

Respiratory symptoms develop in centrally localized tumors, while peripheral LCs are diagnosed incidentally on the chest X-ray. Our reported patient had respiratory infection signs and dyspnea caused by centrally located tumor. The carcinoid syndrome develops in 2–5% of LCs, usually in the metastatic tumor type. The Cushing syndrome is registered in 1–6% of the affected patients [9]. The patient in our study had none of either syndrome characteristics related to hormonal hyperreactivity.

The gold standard for radiological LC detection is the contrast CT. Carcinoids usually appear as round or oval lesions with unclear or lobular margins; around 10% of the patients may develop multiple, bilobar lesions; in that case, they are always associated with calcifications [10]. The diagnostic algorithm required bronchoscopy. To obtain the mediastinal lymph node, transbronchial biopsy sample is required, which enables a precise disease staging. Real-time endobronchial ultrasound bronchoscopy has been recommended over the last decade. The latest invasive diagnostic methods also include fluorescent bronchoscopy, which precisely determines the respectability border [11, 12].

PET is strongly indicated when a local or metastatic spread of the disease, particularly AC, is suspected [13]. Our reported patient, in whom ultrasound and CT screening of the abdomen failed to establish the etiology of new liver lesions three years after the surgery, the erythrocyte pool liver scintigraphy was performed first. The MRI finding of February 2016 revealed the presence of multiple liver deposits characterized as secondary deposits. The patient was submitted to whole-body PET, disclosing active nodes in the liver and an active lesion in the right lung.

About 80% of LCs express the somatostatin-type receptor-2 and -5 (SSTR-2 and SSTR-5). In our patient, after brachytherapy as an endoscopy procedure which ablated the relapsed tumor in the right main bronchus, first line chemotherapy was applied and the patient got a few months of disease stability. When relapse of the disease occurred in the tracheobronchial tree and the liver lesions also progressed in number and size, having obtained the positive octreoscan finding, the patient was started on lanreotide injections.

TC has an excellent prognosis with the 10-year survival of over 90%, while AC is more aggressive, having a higher metastatic potential, worse prognosis, and the 10-year survival less than 60% [14, 15]. Surgical resection is the treatment of choice for patients with LCs. Advanced AC is more aggressive than TC and requires a multidisciplinary meeting review for all medical treatment decisions. The surgical treatment is not indicated in case of advanced or metastatic LCs.

European Society of Medical Oncology guidelines are similar to those of the National Comprehensive Cancer Network and recommends systemic therapy for advanced or metastatic LCs; no preferred regimen; options include cisplatin/etoposide, temozolomide with or without capecitabine, sunitinib, or everolimus; consider octreotide for symptoms of malignant carcinoid syndrome [16, 17]. The treatment with somatostatin analogues is the most frequent second-line systemic approach for patients with advanced or metastatic LCs.

Laser bronchoscopy and other invasive endoluminal procedures such as cryotherapy, argon plasma cauterization, electrocauterization, should be considered for inoperable patients or performed as a preoperative unclogging procedure. Everolimus is an mTOR kinase inhibitor which is indicated for progressive, well-differentiated, non-functional neuroendocrine tumors of lung origin that are locally advanced or metastatic [18, 19].

In the long-term course of the disease, our patient has been treated according to all the above-mentioned European and world treatment guidelines. After the applied palliative interventional bronchoscopy procedures, the patient's survival was prolonged probably due to reduced recurrent post-obstructive pneumonia. Prolonged survival was probably achieved by the use of other therapeutic modalities such as cisplatin/etoposide chemotherapy, somatostatin analogues, and, lastly, the use of everolimus.

Conflict of interest: None declared.

REFERENCES

1. Schnabel PA, Junker K. Pulmonary neuroendocrine tumors in the new WHO 2015 classification: Start of breaking new grounds? Pathologe. 2015; 36(3):283–92.
2. Travis W. Pathology and Diagnosis of Neuroendocrine Tumors. Thorac Surg Clin. 2014; 24(3):257–66.
3. Naalsund A, Rostad H, Strøm E, Lund M, Strand T. Carcinoid lung tumors – incidence, treatment and outcomes: a population-based study. Eur J Cardiothorac Surg. 2011; 39(4):565–9.
4. Swarts D, Ramaekers F, Speel E. Molecular and cellular biology of neuroendocrine lung tumors: Evidence for separate biological entities. Biochim Biophys Acta. 2012; 1826(2):255–71.
5. Hamad A, Rizzardi G, Marulli G, Rea F. Nodal Recurrence of Pulmonary Carcinoid 30 Years After Primary Resection. J Thorac Oncol. 2008; 3(6):680–1.
6. Hallet J, Law C, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: A population-based analysis of epidemiology, metastatic presentation, and outcomes. Cancer. 2014; 121(4):589–97.
7. Tsuta K, Liu D, Kalhor N, Wistuba I, Moran C. Using the Mitosis-Specific Marker Anti–Phosphohistone H3 to Assess Mitosis in Pulmonary Neuroendocrine Carcinomas. Am J Clin Pathol. 2011; 136(2):252–9.
8. Ma X, Wu Y, Zhang T, Song H, Jv H, Guo W, et al. Ki67 Proliferation Index as a Histopathological Predictive and Prognostic Parameter of Oral Mucosal Melanoma in Patients without Distant Metastases. J Cancer. 2017; 8(18):3828–37.
9. Rivera M, Detterbeck F, Mehta A. Diagnosis of lung cancer: the guidelines. Chest. 2003; 123(1):129S–136S.
10. Meisinger Q, Klein J, Butnor K, Gentchos G, Leavitt B. CT Features of Peripheral Pulmonary Carcinoid Tumors. AJR Am J Roentgenol. 2011; 197(5):1073–80.
11. Dooms C, Muylle I, Yserbyt J, Ninane V. Endobronchial ultrasound in the management of nonsmall cell lung cancer. Eur Respir Rev. 2013; 22(128):169–77.
12. Hashmi H, Vanberkel V, Bade BC, Kloecker G. Clinical presentation, diagnosis, and management of typical and atypical bronchopulmonary carcinoid. JCSO. 2017; 15(6):303–7.
13. Baum R, Prasad V, Hommann M, Hörsch D. Receptor PET/CT Imaging of Neuroendocrine Tumors. Recent Results Cancer Res. 2008; 170:225–42.
14. Jovanovic M, Zivaljevic V, Diklic A, Slijepcevic N, Tausanovic K, Stevanovic K, et al. Adrenocortical carcinoma's incidence and mortality in central Serbia. Srp Arh Celok Lek. 2017; 145(1–2):38–42.
15. Cao C, Yan T, Kennedy C, Hendel N, Bannon P, McCaughan B. Bronchopulmonary Carcinoid Tumors: Long-Term Outcomes After Resection. Ann Thorac Surg. 2011; 91(2):339–43.
16. Oberg K, Hellman P, Ferolla P, Papotti M. Neuroendocrine bronchial and thymic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012; 23(suppl 7):vii120–3.
17. Isenberg-Grzeda E, MacGregor M, Bergel A, Eagle S, Espi Forcen F, Mehta R, et al. Antidepressants appear safe in patients with carcinoid tumor: Results of a retrospective review. Eur J Surg Oncol. 2018; 44(6):744–9.
18. Yao J, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016; 387(10022):968–77.
19. Fazio N, Buzzoni R, Delle Fave G, Tesselaar ME, Wolin E, Van Cutsem E, et al. Everolimus in advanced, progressive, well-differentiated, non-functional neuroendocrine tumors: RADIANT-4 lung subgroup analysis. Cancer Sci. 2018; 109(1):174–81.

Метастатски атипични плућни карциноид третиран комбинованим терапијама

Ненси Лалић[1,2], Драгана Тегелтија[1,2], Иван Кухајда[1,2], Сања Томић[2], Ивица Лалић[3,2]

[1]Институт за плућне болести Војводине, Сремска Каменица, Србија;
[2]Универзитет у Новом Саду, Медицински факултет, Катедра за здравствену негу, Нови Сад, Србија;
[3]Клинички центар Војводине, Клиника за ортопедску хирургију и трауматологију, Нови Сад, Србија

САЖЕТАК

Увод Плућни карциноиди чине ретку групу плућних тумора са заступљеношћу око 1% свих примарних плућних тумора. Атипични карциноид плућа је агресивнији у односу на типични, са већом могућношћу метастазирања и лошијом прогнозом, а 10-годишње преживљавање је мање од 60%.

Приказ болесника Године 2012. код 61-годишњег болесника урађена је десна доња лобектомија, а дефинитивни патохистолошки налаз је одговарао атипичном плућном карциноиду у почетном стадијуму болести. Почетком 2016. године радиолошки и бронхоскопски је потврђен рецидив болести у бронху. Магнетна резонанца абдомена потврдила је присуство нодуларних лезија које су одговарале јетреним метастазама. Болесник је тада примио брахитерапију захваћеног дела бронхијалног стабла и хемиотерапију по протоколу цисплатин/етопозид. У августу 2016. године сцинтиграфија соматостатинским рецепторима је показала експресију ових рецептора у плућима и јетри и болесник је отпочео терапију са хемиотерапеутиком ланреотиде. После пет циклуса ове терапије јавила се нова прогресија болести у бронхијалном стаблу, те се урадила електрокаутеризација и аргон-плазма каутеризација тумора. Нова прогресија болести настала је у септембру 2017. године, када је болесник започео терапију са леком еверолимус.

Закључак Оптимални терапијски водичи за лечење атипичног плућног карциноида нису утврђени, а нови објављени радови указују на неопходност његовог мултимодалитетног лечења, чиме се омогућава дуже преживљавање ових болесника.

Кључне речи: плућа; атипични карциноид; соматостатински рецептори; брахитерапија; еверолимус