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Metastatic atypical lung carcinoid treated with combined therapeutic modalities

Метастатски атипични плућни карциноид третиран комбинованим терапијским модалитетима

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SUMMARY

Introduction Lung carcinoid's are considered a rare and uncommon group of lung tumors making about 1% of all primary lung tumors. Atypical carcinoid is more aggressive than typical, 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 atypical lung carcinoid. At the beginning of 2016, a radiological and bronchoscopic progression of the disease was reported. The 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 protocol was applied. In August 2016, the somatostatin receptor (SSNR) scintigraphy revealed secondary deposits with SSNR 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 atypical lung carcinoid is lacking but the recent publications indicate that the multimodal treatment is associated with a prolonged survival.

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

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 већим потенцијалом метастазирања и лошијом прогнозом, 10-годишње преживљавање је мање од 60%.

Приказ болесника Године 2012. код болесника мушког пола урађена је десна доња лобектомија, дефинитивни патохистолошки налаз је одговарао атипичном плућном карциноиду у почетном стадијуму болести. Почетком 2016. г. 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. г. сцинтиграфија соматостатинским рецепторима (ССНР) показала је експресију ССНР у плућима и јетри, пацијент отпочиње терапију са хемиотерапеутиком ланреотиде. Након пет циклуса ове терапије јавља се нова прогресија болести у бронхијалном стаблу те се уради електрокаутеризација и аргон пласмакаутеризација тумора. Нова прогресија болести настаје у септембру 2017. г. када болесник започиње терапију са леком еверолимусом.

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

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

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). This

subdivision is based on the cytomorphological/histomorphological classificastion, nucleus features, and mitosis count. The guidelines for the Ki-67 proliferation rate are given in the new WHO classification as the Ki-67 index which amounts to 50-100% for SCLC, ranges from 40-80% for LCNEC, or from 5-20% for AC, and falls below 5% for TC [1]. Lung carcionoids (LC) are rare pulmonary tumors making 1-5% of all malignant lung tumors, having the incidence of 5 -10/1,000,000 [2]. LCs are less aggressive than other lung carcinomas. The standard treatment approach for lung carcinoid is a surgery, due primarily to the fact these tumors are poorly sensitive to irradiation or chemotherapy [3].

TCs make 70-90%, and ACs make 10-30% of all LCs. The overall survival of patients undergoing a total TC resection amounts to 92-100%, or 61-88% for a totally resected AC. Inoperable LCs represent a great 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

A 54-year 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 right hilus lower pole (Figure 1). The chest computed tomography (CT) finding disclosed a tumor 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, obstructing almost totally the basal bronchi. The histologic finding of the tumor biopsy sample correlated to lung adenocarcinoma. On 12 November 2012, the patient was submitted to anterolateral thoracotomy and lobectomy of the right lower lung lobe. The definite histopathology finding was tumor carcinoides typus atypicus (Figure 2) - sized 3.5 cm. The TNM classification established the definite T2aN0M0 stage of the disease. Regular postoperative Oncology Board controls were performed. All required analyses persisted normal for 3 years.

On the regular control in November 2015, the patient had no symptoms, chest X-ray was identical to the former one, but computed tomography 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 was presented with tiny inhomogeneous lesions in the right upper lung field and CT of the thorax disclosed infiltrative, inflammatory-type lesions at S2 on the right, accompanied with an atypical consolidation, an intraluminal lesion of the intermediary bronchus. Unclearly demarcated liver lesions were also detected. The MRI finding of February 2016 was presented with multiple liver lesions characterized as secondary deposits. The whole-body positron emission tomography (PET) was performed revealing active nodes in the liver and an active lesion in the right lung (Figure 3).

Bronchoscopy performed in February 2016 with following finding: Tiny tumor formations, smooth in the distal part of the trachea and one larger smooth tumor in the orifice for the upper bronchus on the right, entirely obstructing the orifices. The Oncology Board prescribed endoluminal irradiation treatment to be followed by chemotherapy (cisplatin/etopozid protocol). The patient completed this treatment in July 2016. On the control examination in August 2016, the finding on the lungs was in a partial regression, but the finding on the liver persisted unchanged. All available histopathological were reassessed and all samples were atypical carcinoid of the lung with low proliferative Ki index. The somatostatic receptor scintigraphy was performed showing secondary deposits with SSNR expression in the liver and lungs. The patient started to take 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).

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 atypical carcinoid, introducing the treatment with a drug everolimus. 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 from 0.2 to 2/100.000 people/year in the USA and Europe [6]. LCs belong to neuroendocrine lung tumors staged from the low-grade typical carcinoid (TC) and intermediate-grade atypical carcinoid (AC), to the high-grade large cell neuroendocrine cancer (LCNEC), and small cell lung cancer (SCLC). TCs have less than 2 mitoses/2 mm2, and no necrosis, while ACs have 2-10 mitoses/2mm2, 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 Ki-67 proliferative index introduced in the clinical practice in 2015 by the new WHO classification fore NET's tumors, ranging from 5-20% for AC and amounting to <5% for TC. The Ki-67 proliferative index in our patient's sample amounted to 15%, which additionally confirmed the IHA findings of AC.

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 Chushing syndrome is registered in 1-6% of the affected patients [8]. The patient in our study had none of either syndrome characteristics related to hormonal hyperreactivity.

The golden standard for radiological LC detection is the contrast computerized tomography (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 [9]. The diagnostic algorithm required bronchoscopy. To obtain the mediastinal lymph node transbronchial biopsy sample is require, which enables a precise disease staging. The real time EBUS bronchoscopy has been

recommended over the last decade. The latest invasive diagnostic methods also include fluorescent bronchoscopy, which precisely determines the respectability border [10]. In peripheral lesions, the biopsy sample may be obtained by radioscopy guided transthoracic biopsy, or using the radial EBUS, or by CT-guided transthoracic puncture. It should be noted these are small biopsy samples, so differentiation from other lung tumors is reduced, as well as differentiation between TC and AC [11].

PET is not applied in routine diagnostics, but it is strongly indicated when a local or metastatic spread of the disease, particularly AC, are suspected [12]. Our reported patient, in whom the US and CT screening of the abdomen failed to clearly 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 positron emission tomography of the whole body (PET) disclosing active nodes in the liver and an active lesion in the right lung.

About 80% of LCs express the somato-statin 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 applied andpatient got a few months long period of the disease stability. When relapse of the disease occurred in the tracheobronchial tree again, and the liver lesions also progressed in number and size, having obtained the positive octreoscan finding, the patient started to take lanreotide injections.

Typical carcinoid has an excellent prognosis with the 10-year of over 90%, while atypical carcinoid is more aggressive, having a higher metastatic potential, worse prognosis, and the 10-year survival < 60% [13, 14]. 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.

Systemic chemotherapy (CT) should be used in case of advanced unresectable, recurrent or metastatic LCs. European Society of Medical Oncology (ESMO) guidelines are similar to those of the National Comprehensive Cancer Network (NCCN) and recommends systemic therapy; no preferred regimen; options include cisplatin/etoposide, temozolomide with or without capecitabine, sunitinib, or everolimus; consider octreotide for symptoms of

malignant carcinoid syndrome [15]. The treatment with somatostatin analogues (SSAs) is the most frequent second-line systemic approach for patients with advanced or metastatic LCs. Due to their excellent safety profile, SSAs (lanreotide drug) should be considered as systemic treatment of patients with advanced LCs of low proliferation index.

Laser bronchoscopy and other invasive endoluminal procedures such as cryotherapy, argon plasma cauterization, elecrtocauterisation should be considered a suboptimal treatments for inoperable patients or performed as a preoperative desopstructive procedures. Everolimus is an mTOR kinase inhibitor (mammalian target of rapamycin, a serine-threonine kinase, downstream of the PI3K/AKT pathway, which is dysregulated in several human cancers. It is indicated for progressive, well-differentiated, non-functional NET of lung origin that are unresectable, locally advanced or metastatic [16].

In the long-term course of the disease, our patient is treated according to all the above mentioned European and world treatment guide lines.

Conflict of Interest: None declared.

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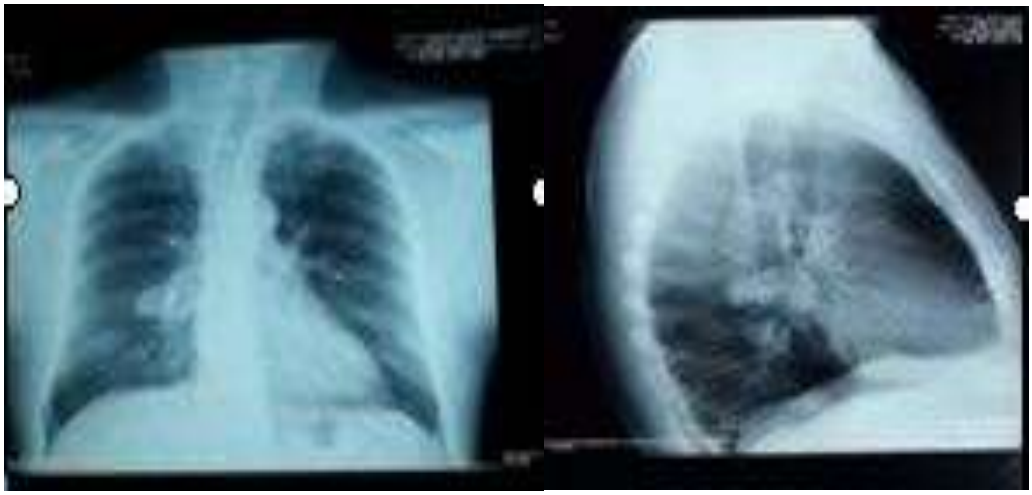

Figure 1. Chest X-ray finding: an oval opacity at the right hillus lower pol

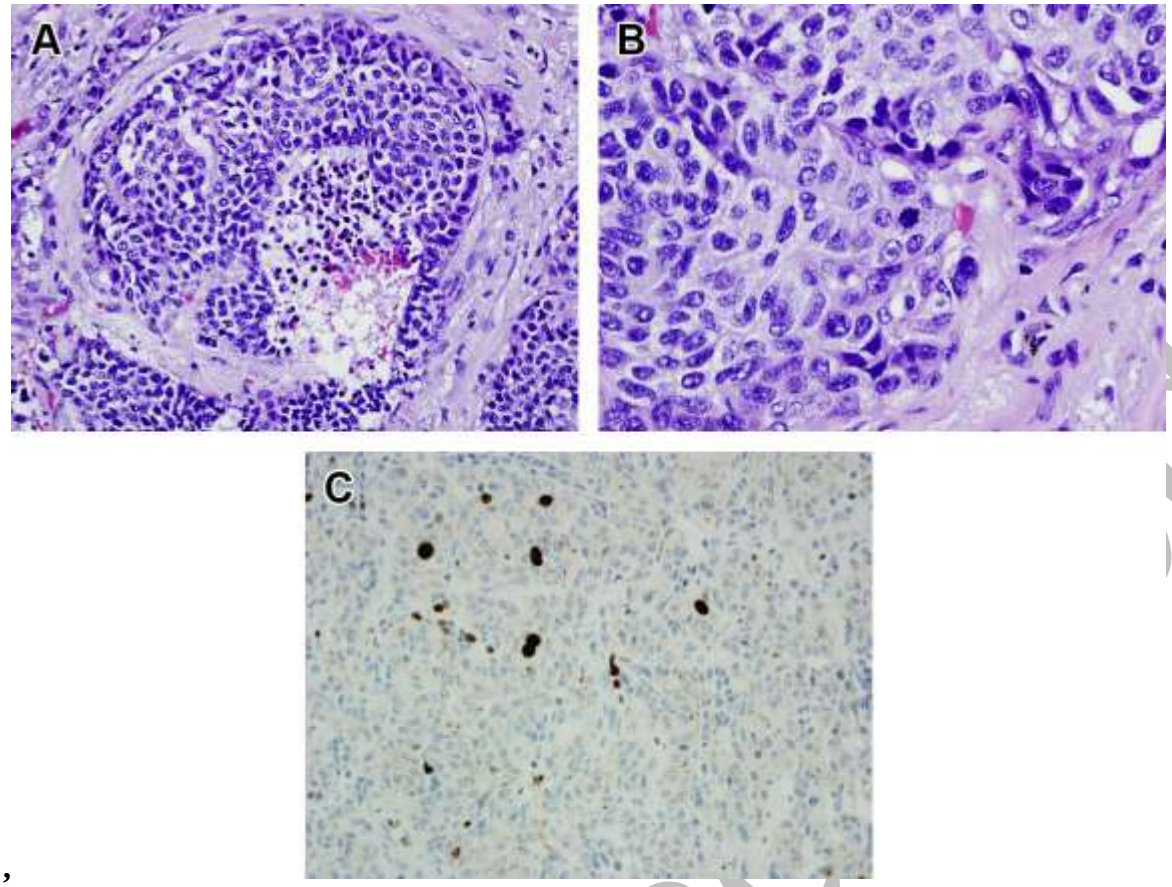

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Figure 2. Atypical carcinoid; (A) punctate focus necrosis of carcinoid tumor cells and eosin; (B) a single mitosis in one tumor cell and cells with granular nuclear chromatin; (C) Ki-67 shows an intermediate proliferation rate

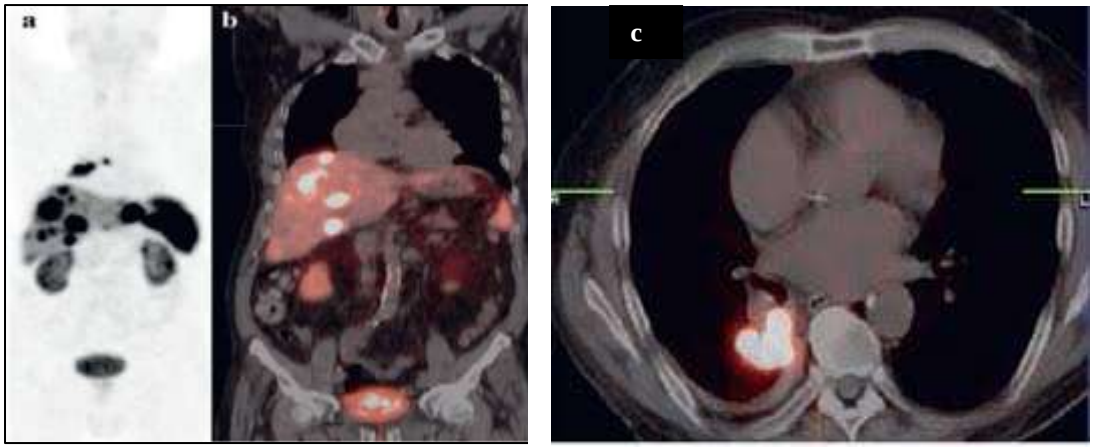

Figure 3. MRI of the abdomen: detected liver lesions correlate to metastatic, confirmed by PET, which showed accumulation of radioactive fluorodeoxyglucose in liver and lung

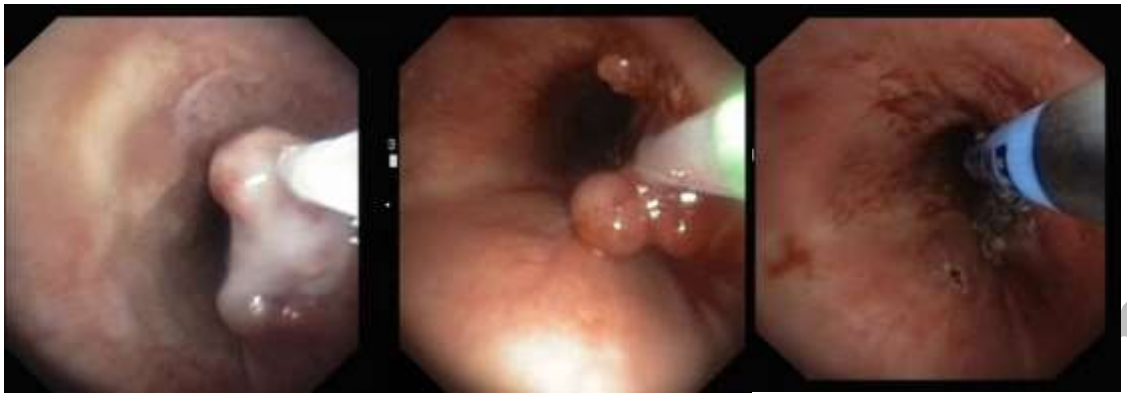

Figure 4. Endoscopic finding - The tumor removed applying the electrocautery loop. Infiltrations in the tracheobronchial tree removed by argon plasmcauterization

