

PULMONARY TUMORLETS WITH SURROUNDING FIBROUS TISSUE – SUSPECTED CARCINOMA: CASE REPORT AND REVIEW OF THE LITERATURE

Ivan Alerić¹, Domagoj Mosler², Sven Seiwert³, Ines Mlinarević Polić⁴ and Elvira Lazić Mosler⁵

¹Clinical Hospital for Pulmonary Diseases, Zagreb University Hospital Center, Zagreb; ²Topusko Spa Center, Topusko; ³Department of Pathology, School of Medicine, University of Zagreb, Zagreb, Croatia; ⁴Mostar University Hospital Center, Mostar, Bosnia and Herzegovina; ⁵Department of Dermatology and Venereology, Dr. Ivo Pedišić General Hospital, Sisak, Croatia

SUMMARY – Pulmonary tumorlets are small, often multiple nodular proliferations of pulmonary neuroendocrine cells. They are common incidental findings in chronic inflammatory pulmonary diseases. They can also be found in normal lung parenchyma and as one part of the continuum known as diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. In many cases, they are incidental histologic findings of no importance or clinical consequences, or they can be associated with a very slow progression of either obstructive or mixed obstructive/restrictive impairment with good prognosis. Only rarely, they metastasize to an adjacent lymph node or produce ectopic neuroendocrine products. When found during diagnostic examination, they represent a doubt to be a malignant tumor until proven otherwise, which is often impossible without biopsy or surgical removal of the adjacent lung lobe. Hereby, we present a patient with a persistent nodular lung structure after being treated for nonspecific symptoms, cough with non purulent sputum and pain among the scapulae, for a period of one month. He had otherwise normal clinical and laboratory findings, except for a mild mixed obstructive/restrictive pattern of impairment that was shown by lung spirometry. After 8 months, he underwent lobectomy of the medial lobe of the lung with partial lymphadenectomy, since the diagnostic methods applied could not define the nature of lung nodular infiltration. Histologic examination showed a few tumorlets surrounded by the fibrous tissue with a very dense lymphocyte infiltration. We present a review of the literature and emphasize the necessity to include tumorlets with adjacent fibrosis as part of the differential diagnosis of a solitary nodular lung structure.

Key words: *Solitary pulmonary nodule; Pulmonary coin lesion; Lung neoplasms – diagnosis; Carcinoid tumor; Case report*

Introduction

Pulmonary tumorlets are nodular proliferations of pulmonary neuroendocrine cells (PNCs), sized less than 5 mm in diameter. They are often multiple and

usually peripheral and are common incidental findings in chronic pulmonary diseases such as bronchiectasis and chronic lung abscess¹⁻³. They can also be found in normal lungs^{2,4} and as one part of the continuum of diffuse idiopathic PNC hyperplasia (DIPNECH)⁵⁻⁸. In many cases, they are of no clinical importance or consequences, or they can be associated with a very slow progression of either obstructive or mixed obstructive/restrictive impairment with good prognosis^{5,8,9}. Only rarely, they metastasize^{1,10,11} or produce

Correspondence to: *Assist. Prof. Ivan Alerić, MD, PhD*, Clinical Hospital for Pulmonary Diseases, Zagreb University Hospital Center, Jordanovac 104, HR-10000 Zagreb, Croatia
E-mail: i.aleric@inet.hr

Received October 2, 2012, accepted March 14, 2014

ectopic neuroendocrine products^{9,11-13}. When found during clinical examination and investigation, especially by different imaging analyses, they represent a doubt to be a malignant tumor until proven otherwise, which is often impossible without biopsy and, even more, without surgical removal of the adjacent lung lobe^{8,14}.

Including tumorlets with their adjacent fibrosis in the differential diagnosis of a solitary nodular structure, and thereby supposing them to be a possible lung carcinoma, can help clinicians decide to either include radical treatment or to keep on with watchful waiting.

Case Report

A 79-year-old male patient was referred to the hospital after he had suffered from cough with non purulent sputum for three weeks. During the last few days before admission, he was subfebrile with chilliness and shivering, as well as interscapular pain. The patient past history revealed that he stopped smoking 39 years before, after he had smoked 15 cigarettes during the period of ten years. Also, in the last ten years, he had been treated for arterial hypertension. Physical

examination revealed normal breathing sounds and laboratory data were also normal. His lung spirometry showed a mild mixed obstructive/restrictive pattern of impairment, while x-ray discovered a solid, solitary nodular lesion of 15 mm in diameter in the basal middle lobe. After administration of two antibiotics, there was no complete regression of symptoms and he underwent computerized tomography (CT) of the chest (Fig. 1), which confirmed a 15-mm solid solitary nodular lesion surrounded by ground-glass opacity forming a halo sign, dragging towards the oblique interlo-

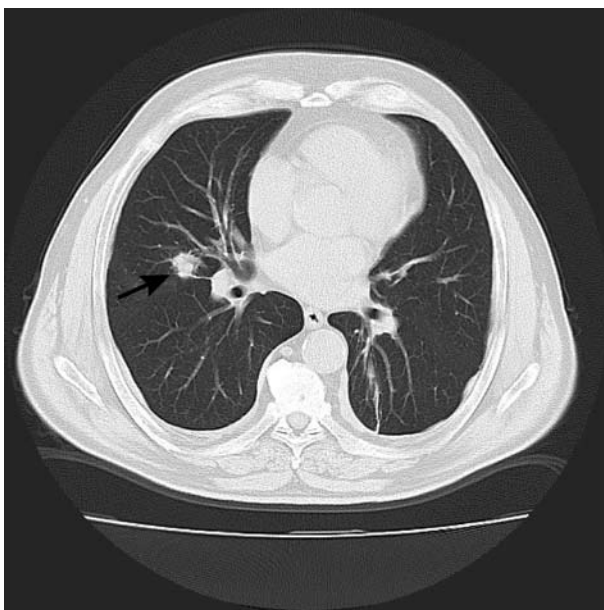


Fig. 1. Computed tomography horizontal section of the chest showing a 15-mm solid solitary nodular lesion surrounded by ground-glass opacity forming a halo sign, dragging towards the oblique interlobium.



Fig. 2. (A) Fused frontal whole-body positron-emission tomography-computed tomography (PET-CT) showing intensive accumulation of the radiotracer in the nodular structure of the medial lung lobe; (B) horizontal section PET-CT showing less intensive accumulation in the part of the corticalis of the upper part of the left femur.

bium. CT of the upper abdomen was normal. In the course of the next few months, the patient underwent further follow up analyses, including four fiberbronchoscopies, once x-ray guided, in order to obtain samples by brush smear and cytologic catheter aspiration. All laboratory findings were normal, including tumor markers: progastrin-releasing peptide (ProGRP) 35.115 pg/mL, cytokeratin 19 fragment (CYFRA 21-1) 2.430 ng/L and neuron-specific enolase (NSE) 9.4 µg/L. Since follow up chest x-rays 3 months later showed progression of the lesion to the size of 20 mm, positron emission tomography-CT (PET-CT) of the whole body to the proximal parts of the thighs, as well

as CT of the head, neck, thorax and abdomen with oral and intravenous application of contrast were performed. The former showed intensive accumulation of radiotracer in the known nodular structure of the medial lung lobe (Fig. 2A) and less intensive accumulation in the part of the corticalis of the upper part of the left femur (Fig. 2B). The latter showed only several lymph nodes up to 12 mm in diameter, both in the axillae and mediastinum. In the medial lobe towards the border to the upper lobe, a lobulated, irregularly shaped, spiculated, expansive lesion (24x21x25 mm) was shown, which probably infiltrated the horizontal and oblique interlobium. Near this structure, there

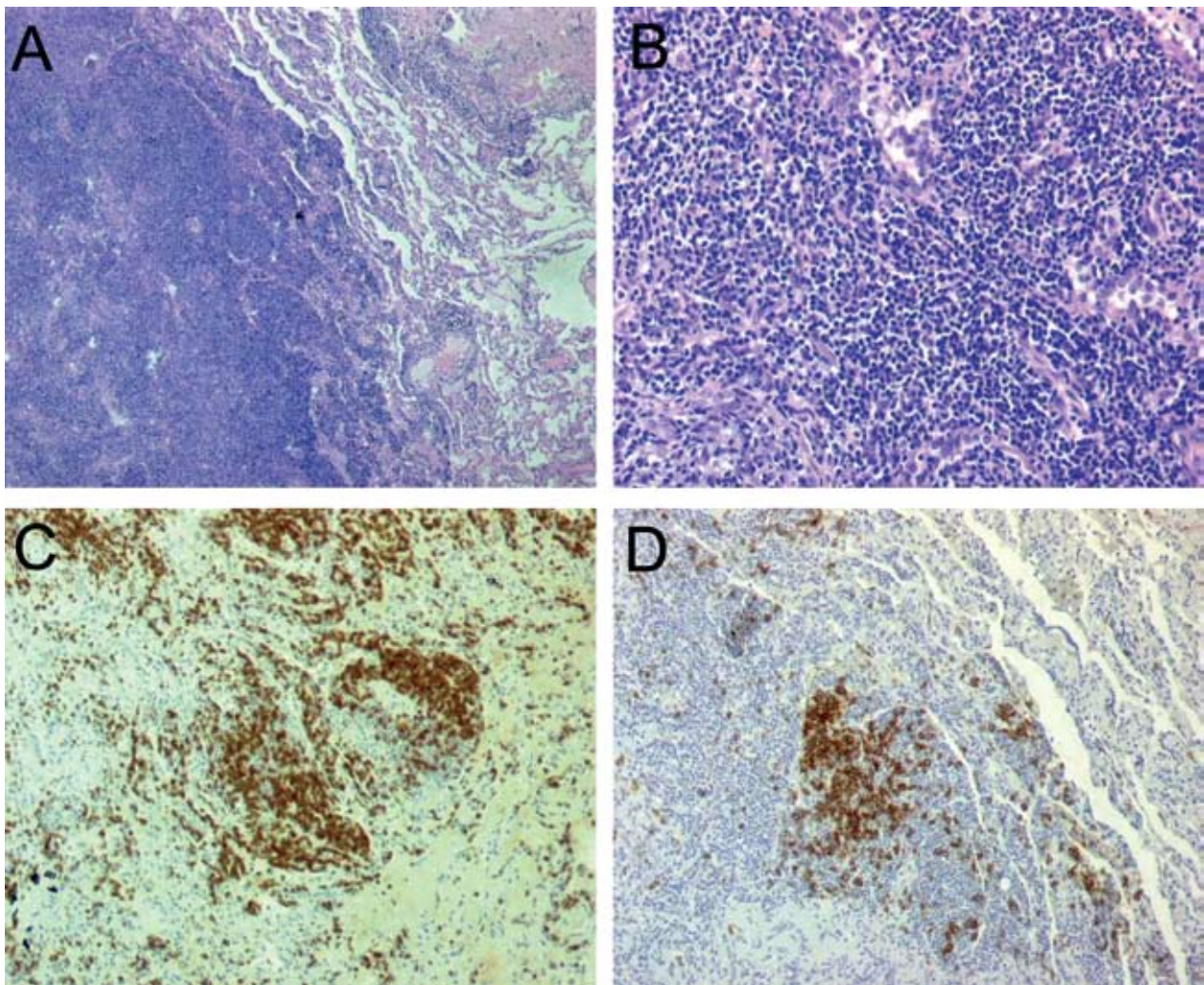


Fig. 3. Hemalaun-eosin stained slides under objective X4 (A) and X20 (B) showing a relatively sharply demarcated area of predominantly mononuclear inflammatory infiltrate with some reactive connective tissue. Immunohistochemistry demonstrated predominantly CD 3 (C) positivity of inflammatory cells, with foci (D) of CD 20 positive cells.

were several smaller nodular satellite lesions up to 6 mm in diameter. The lesion of the corticalis was also seen. Two months later, at the same position, follow up CT of the thorax showed an irregular solid nodular structure of 20 mm in diameter, consisting of areas of different densities. Eight months after his first referral, the patient underwent right thoracotomy and medial lobectomy with dissection of 8 peribronchial and 13 mediastinal lymph nodes. Histologic examination of the lung tissue revealed poorly defined borders of whitish-gray area of 3 cm in diameter, with fibrous tissue augmentation and dense lymphocyte infiltration (Fig. 3A, B). Few small microscopic nodules were shown along one large blood vessel. After immunohistochemical analysis (Fig. 3C) demonstrated predominantly CD3 positivity of inflammatory cells with foci of CD20 positive cells (Fig. 3D), together with thyroid transcription factor (TTF)-1 and CD56 positive cells, the diagnosis of a tumorlet was made. Histologic analysis of dissected lymph nodes showed no tumor metastases. There were no complications in the postoperative course and the patient was discharged 9 days after surgical intervention. The lesion of the corticalis shown on both of PET-CT and CT was considered as a result of degenerative change^{15,16}. The patient had an uneventful postoperative course and follow up period for more than 4 years, without administration of any adjuvant treatment.

Discussion

Pulmonary tumorlets are islet-like extraluminal proliferations of PNCs, also known as Kulchitsky cells, which are normally found in bronchial and bronchiolar mucosa⁴. Tumorlets are currently diagnosed more frequently, mainly due to the extensive use of advanced radiological techniques. According to the World Health Organization's classification of lung tumors, they are defined as tumorlets by size of 2 to 5 mm, as part of a continuum named DIPNECH, which begins with generalized proliferation of scattered single cells and extends to the carcinoid tumors, which are greater than 5 mm in diameter⁵. The same classification of DIPNECH excludes another kind of PNC proliferation, also in the form of a tumorlet or carcinoid, which can be found in different chronic pulmonary diseases, such as bronchiectasis and chronic lung abscess, often together with a pe-

ripheral carcinoid¹⁻³. Formerly, tumorlets were associated only with chronic inflammatory lung processes, mostly because they were revealed *post mortem* during autopsy of patients who died from such diseases. Whitwell, who coined the term 'tumorlet', postulated bronchiectasis or lung abscess as the only origin of a tumorlet in 73 per cent of 24 reported cases³. The most probable causes of such kind of PNC 'secondary' proliferation are hypoxia and chronic inflammation, which stimulate the proliferation of neuroendocrine cells^{1,2,17}. Other authors have reported a kind of dichotomy regarding the state of lung in which tumorlets were found: among 20 cases of pulmonary tumorlets, one-third occurred in lungs severely scarred by chronic inflammatory processes, whereas the other two-thirds were found in lungs with little or no scarring². According to Gosney and Travis, this latter kind of 'primary' proliferation of PNCs, which occurs in otherwise normal lungs^{4,6-8,13}, is distinguished as DIPNECH⁵. This entity was well defined by Aguayo *et al.* in 1992⁶, many years after recognition and publishing its features. The origin and cause of primary proliferation of PNCs to DIPNECH is yet unknown. There are no genetic markers that might distinguish these two kinds of proliferation of PNCs. There is, however, 11q13 allelic imbalance that was found by a group of authors, which can be a discriminatory marker being very rare in tumorlets while present in most of carcinoids¹⁸. It is interesting that progression of proliferation from a tumorlet to carcinoid tumors does not occur in chronic inflammatory lung processes as it does in the course of DIPNECH^{5,18}. The connective tissue reaction is characteristic of both types of PNC proliferation. In DIPNECH, secondary fibrosis is a result of proliferated PNCs, which causes and stimulates inflammation with proliferation of fibroblasts, leading to the synthesis of collagen and resulting in bronchiolar occlusion and extramural fibrosis of the involved airway in otherwise unremarkable surrounding lung tissue^{5,6,19}. Secondary PNC proliferation occurs in the areas of pulmonary fibrous lesions as a response to chronic inflammatory and fibrotic processes^{2,3,10,19}. So far, we have seen tumorlets as part of the continuum of primary PNC proliferation called DIPNECH. However, it has to be mentioned that D'Agati and Perzin have presented a case report describing tumorlets that were revealed in end-stage

lung disease caused by bronchiectasis, chronic bronchitis and pulmonary fibrosis. Those tumorlets were found in a spectrum of pathologic changes ranging from intramucosal proliferation of PNCs to the microscopic tumorlet. Consequently, they suggest that pulmonary tumorlets should be viewed as part of a biologic spectrum of PNC proliferation, this time a secondary one¹⁰.

Therefore, we find it convincing that numerous data imply that the present nosologic concept of tumorlets, including clinical, malignant, etiopathogenic, morphological, prognostic, paraneoplastic and genetic aspects, and especially those regarding differences from carcinoid, should be additionally clarified^{2,7,11,18}. Also, the context in which the tumorlet occurs regarding otherwise normal lung, DIPNECH and chronic inflammatory disease, should be further researched¹⁰.

Earlier, tumorlets were categorized as small, multifocal, peripherally situated minute lesions of less than 5 mm in size^{3,9,20}, unlike the carcinoid, which is greater than 5 mm and located centrally^{10,19}. However, some recent studies have shown that the location of a tumor is not a defining characteristic^{8,21,22}. They are reported to be found more often in the fifth and sixth, or even seventh decade and among women^{2,3,8,13,23}, but their precise incidence is not certain. Tumorlets were found at autopsy in 2 out of 1900 patients with no previous lung disease, and in 22 out of 2400 lung samples resected for various causes in one, and 17 of 7800 autopsies in another study^{2,3}. They were also found in 5 lungs from a series of 35 autopsies¹³.

Tumorlets are most often a slow growing incidental finding at histopathologic analysis, mostly found after autopsy or after resection of lung parenchyma for various reasons^{2,3}. There is more clinical significance and relevance when they are detected as nodal structures during radiological analysis, which is sometimes, but not always indicated. That is why there is often no definite answer if they are in any association or even more causative connection with the clinical status of the patient. The presenting symptoms, if there are any, depend on the constellation in which the tumorlets arise. If it is primary PNC proliferation, i.e. DIPNECH, many cases remain asymptomatic with no clinical consequences or with very slowly worsening dry cough and breathlessness in the course

of many years, associated with very slow progression of obstructive or mixed obstructive/restrictive impairment with good prognosis^{5,7-9}. Some new emerging data associate multiple tumorlets within DIPNECH with severe emphysema or obliterative bronchiolitis^{6,8}, and in one reported case of progressive airflow limitation even with underlying obliterative bronchiolitis successfully treated by single lung transplantation²⁰. The predominant symptoms of secondary PNC proliferation are consequential to the underlying disease. Since tumorlets are focal proliferation of PNCs, it is expected that they can produce different molecules and hormones, which Gosney *et al.* describe as appropriate and inappropriate neuroendocrine products, since some of them are normally found in PNCs, like proGRP, calcitonin or serotonin, and some of them are not, like adrenocorticotrophic hormone (ACTH), vasoactive intestinal polypeptide, growth hormone, antidiuretic hormone and somatostatin^{4,11-13}. Consequently, they may present with symptoms of ectopic hormone secretion like Cushing syndrome caused by ectopic secretion of ACTH^{8,9,11,19,24}. Tumorlets only rarely metastasize, but there are few documented patients with peribronchial, hilar, mediastinal or axial lymph node metastases^{1,8,10,11,19,25}.

With or without the presenting symptoms, when detecting solitary or multiple pulmonary nodules after initial radiologic analysis, i.e. chest radiography, and them being confirmed by CT and PET/CT, as in the case presented, many different diagnostic and treatment options arise. There are many differential diagnoses for a solitary pulmonary nodule, but the priority is to exclude malignancy like small cell lung cancer. Pulmonary tumorlets are often situated peripherally, which makes them unsuitable for bronchoscopic analysis including biopsy, catheter aspiration and brush smear. Furthermore, they are small and unreachable to percutaneous ultrasound or CT-guided fine needle aspiration. Finally, there are many cases that end in surgical treatment after sophisticated diagnostic methods not being able to exclude malignancy⁸.

Conclusion

The presented case demonstrates that pulmonary tumorlets with the surrounding fibrous tissue, when

found in otherwise normal lungs, should be considered in differential diagnosis of solitary pulmonary nodules visualized by CT and confirmed by PET/CT. In the case presented, the short period of observation was also due to the lesion of the corticalis of the left femur, as seen on PET/CT, raising suspicion of a distant metastasis, which led to surgical treatment.

References

1. DOGAN R, KARA M, GUNDOGDU AG, FIRAT P. An underrated potential risk of bronchiectasis: lymph node metastasis of a pulmonary tumorlet. *Acta Chir Belg* 2009;109:109-11.
2. CHURG A, WARNOCK ML. Pulmonary tumorlet: a form of peripheral carcinoid. *Cancer* 1976;37:1469-77.
3. WHITWELL F. Tumorlets of the lung. *J Pathol Bacteriol* 1955;70:529-41.
4. GOSNEY JR, SISSONS MC, ALLIBONE RO. Neuroendocrine cell populations in normal human lungs: a quantitative study. *Thorax* 1988;43:878-82.
5. GOSNEY J, TRAVIS WD. Pathology and genetics: tumors of the lung, pleura, thymus and heart. In: TRAVIS W, BRAMBILLA E, MULLER-HERMELINK H, *et al.*, editors. *World Health Organization Classification of Tumors*. Lyon, France: IARC, 2004;76-7.
6. AGUAYO SM, MILLER YE, WALDRON JA Jr, *et al.* Brief report: idiopathic diffuse hyperplasia of pulmonary neuroendocrine cells and airways disease. *N Engl J Med* 1992;327:1285-8.
7. MILLER MA, MARK GJ, KANAREK D. Multiple peripheral pulmonary carcinoids and tumorlets of carcinoid type, with restrictive and obstructive lung disease. *Am J Med* 1978;65:373-8.
8. AUBRY MC, THOMAS CF Jr, JETT JR, SWENSEN SJ, MYERS J. Significance of multiple carcinoid tumors and tumorlets in surgical lung specimens: analysis of 28 patients. *Chest* 2007;131:635-43.
9. ARIOGLU E, DOPPMAN J, GOMES M, KLEINER D, MAURO D, BARLOW C, PAPANICOLAOU DA. Cushing's syndrome caused by corticotropin secretion by pulmonary tumorlets. *N Engl J Med* 1998;339:883-6.
10. D'AGATI VD, PERZIN KH. Carcinoid tumorlets of the lung with metastasis to a peribronchial lymph node: report of a case and review of the literature. *Cancer* 1985;55:2472-6.
11. LIU SM, WU HH, WU CJ, KUO CL, MO LR. Adrenocorticotropin-producing pulmonary tumorlets with lymph node metastasis. *Pathol Int* 2003;53:883-6.
12. MASUKO H, SATOH H, MIYAZAKI K, KIKUCHI N, KONDO Y, OHTSUKA M, HIZAWA N. Pulmonary sequestration with elevated serum level of progastrin-releasing peptide. *Intern Med* 2008;47:157-60.
13. GOSNEY J, GREEN AR, TAYLOR W. Appropriate and inappropriate neuroendocrine products in pulmonary tumorlets. *Thorax* 1990;45:679-83.
14. ARMBRUSTER C, BERNHARDT K, SETINEK U. Pulmonary tumorlet: a case report of a diagnostic pitfall in cytology. *Acta Cytol* 2008;52:223-7.
15. ROSEN RS, FAYAD L, WAHL RL. Increased 18F-FDG uptake in degenerative disease of the spine: characterization with 18F-FDG PET/CT. *J Nucl Med* 2006;47:1274-80.
16. COSTELLOE CM, MURPHY WA Jr, CHASEN BA. Musculoskeletal pitfalls in 18F-FDG PET/CT: pictorial review. *AJR Am J Roentgenol* 2009;193:WS1-WS13.
17. GOULD VE, LINNOILA RI, MEMOLI VA, WARREN WH. Neuroendocrine components of the bronchopulmonary tract: hyperplasias, dysplasias, and neoplasms. *Lab Invest* 1983;49:519-37.
18. FINKELSTEIN SD, HASEGAWA T, COLBY T, YOUSEM SA. 11q13 allelic imbalance discriminates pulmonary carcinoids from tumorlets. A microdissection-based genotyping approach useful in clinical practice. *Am J Pathol* 1999;155:633-40.
19. RANCHOD M. The histogenesis and development of pulmonary tumorlets. *Cancer* 1977;39:1135-45.
20. HAUSMAN DH, WEIMANN RB. Pulmonary tumorlet with hilar lymph node metastasis: report of a case. *Cancer* 1967;20:1515-9.
21. SHEERIN N, HARRISON NK, SHEPPARD MN, HANSELL DM, YACOB M, CLARK TJ. Obliterative bronchiolitis caused by multiple tumorlets and microcarcinoids successfully treated by single lung transplantation. *Thorax* 1995;50:207-9.
22. ISHIDA T, YOKOYAMA H, SUGIO K, KANEKO S, SUGIMACHI K, HARA N, OHTA M. Carcinoid tumor of the lung: clinicopathological and immunohistochemical studies. *Eur J Surg Oncol* 1992;18:180-7.
23. GINSBERG MS, AKIN O, BERGER DM, ZAKOWSKI MF, PANICEK DM. Pulmonary tumorlets: CT findings. *Am J Roentgenol* 2004;183:293-6.
24. OGO A, ETO T, HIRAMATSU S, WATANABE A, SAKAI Y, YOSHIZUMI H, UESUGI N, NAKAJIMA O. Autopsy of a patient with Cushing's syndrome who was revealed to have pulmonary tumorlets producing ectopic ACTH. *Endocr J* 2007;54(6):863-70.
25. DEMIRAĞ F, ALTINOK T. Pulmonary and peribronchial lymph node tumorlets: report of a case and review of the literature. *Tumori* 2003;89:455-7.

Sažetak

PLUĆNI TUMORLETI S OKOLNIM FIBROZNIIM TKIVOM – SUSPEKTNI KARCINOM:
PRIKAZ SLUČAJA I PREGLED LITERATURE*I. Alerić, D. Mosler, S. Seiwert, I. Mlinarević Polić i E. Lazić Mosler*

Plućni tumorleti su malene, često višestruke nodularne proliferacije plućnih neuroendokrinih stanica te su čest slučajni nalaz kod kroničnih upalnih plućnih bolesti. Također se mogu naći u normalnom plućnom parenhimu te kao jedan dio kontinuuma poznatog kao difuzna idiopatska hiperplazija plućnih neuroendokrinih stanica. U mnogim slučajevima oni su slučajni histološki nalaz bez značenja ili kliničkih posljedica, a mogu biti i povezani s vrlo sporom progresijom opstruktivnog ili miješanog opstruktivno-restriktivnog oštećenja s dobrom prognozom. Samo rijetko metastaziraju u obližnje limfne čvorove ili stvaraju ektopične neuroendokrine produkte. Nađeni tijekom dijagnostičkog pregleda, predstavljaju sumnju na maligni tumor sve dok se ne dokaže suprotno, što je često nemoguće bez biopsije ili kirurškog odstranjenja pripadajućeg plućnog režnja. Prikazuje se bolesnik s ustrajnim čvorom unutar plućnog parenhima nakon što je tijekom mjesec dana bio liječen zbog nespecifičnih simptoma – kašlja bez gnojnog iskašljaja i boli između lopatica. Ostali su klinički i laboratorijski nalazi bili uredni osim blagog miješanog opstruktivno-restriktivnog oštećenja. Nakon 8 mjeseci odstranjen je srednji režanj pluća zajedno s dijelom limfnih čvorova, jer primijenjene dijagnostičke metode nisu mogle odrediti prirodu čvoraste infiltracije pluća. Histološki pregled je pokazao nekoliko tumorleta okruženih fibroznim tkivom uz vrlo gustu infiltraciju limfocitima. U ovom članku donosimo pregled literature te prikaz slučaja koji naglašava neophodnost uključivanja tumorleta s okolnim fibroznim tkivom u diferencijalnu dijagnozu solitarne nodularne strukture u plućima.

Ključne riječi: Solitarni plućni čvorčić; Plućna lezija veličine kovanice; Plućni tumori – dijagnostika; Karcinoidni tumor; Prikaz slučaja