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Primary Amyloid Tumors of the Lungs – Six Cases

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Over a period of nine years, the authors followed up six cases of primary amyloid tumors of the lungs in patients at the mean age of 58.5 years. All the patients were suspected of bronchial carcinoma and they were subjected to surgical treatment. The duration of follow-up varied, but their postoperative status was satisfactory. Immunohistochemical reactions showed deposits of AL amyloid in five cases; in one of these patients, pulmonary amyloid tumors were related to marginal zone lymphoma of the lung. In one case, the accumulated amyloid was transthyretin.

Introduction

Amyloid lesions involving the lungs are most commonly seen in general amyloidosis. In chronic inflammatory processes, the most frequently encountered substance is AA amyloid, observed predominantly in blood vessel walls or focally involving the stroma of the lung. Another type of amyloid seen in generalized pulmonary amyloidosis is AL amyloid observed in the course of neoplastic proliferation, chiefly plasmocytomas and lymphomas. The incidence of pulmonary involvement in generalized amyloidosis is reported as markedly variable, what follows from incomplete autopsy data; the values quoted by various investigators range from several to 92% [2, 3, 8, 41]. In the opinion of the present authors, the high percentage of incidence is more probable. It should be borne in mind however, that pulmonary involvement in generalized amyloidosis is very rarely the main cause of death, so often the lungs of such patients are not tested for amyloid presence [1, 4]. Some problems are associated with several classifications of amyloidoses that are currently in use and the resulting terminology; for example, some forms of localized amyloidosis are divided into nodular, localized, senile or familial, and these groups clearly overlap. A modern classification of amyloidoses must be based on the chemical structure of amyloid [36, 39]. The employment of immunohistochemical techniques in determining the amyloid type has markedly extended our abilities to more precisely classify the lesion, but some technical problems occur in association with using commercially available antibodies, which either detect non-amyloid substances within an amyloid deposit, do not react with the amyloid that constitutes a fragment of a protein employed as an antigen, or else show cross-reactivity [39].

According to Rubinow [37], localized, isolated pulmonary amyloidosis may occur in three forms: as single or multiple nodular lesions situated in the peripheral lung zones, as disseminated, nodular or confluent foci located in the bronchi and trachea, and – in the least common cases – as a diffuse involvement of the pulmonary interstitium by amyloid deposits [2, 12]. In view of its clinical presentation, the nodular form of amyloidosis often raises a suspicion of bronchial carcinoma and requires cytological or histological examination. In the cytological examination, on frequent occasions, despite repeated evaluations, no suspect cells are found, but appropriate assessment of cytology allows for establishing a correct diagnosis [10]. Carcinoma suspicion due to bronchial stenosis may be also caused by the disseminated nodular form of the disease, with amyloid deposits situated in the bronchial walls [31].

Material and Methods

In the period of nine years, between 1996 and 2004, the authors evaluated six patients with amyloidosis presenting with solid pulmonary tumors [32]. Chest radiograms had previously indicated pulmonary tumors in all the individuals. Since cytology and histology of bronchial sections failed to confirm the presence of pulmonary carcinomas, a decision was reached in each case to perform a surgery. Postoperatively, all the patients were doing well and none demonstrated systemic amyloidosis.

Amyloid tumors involving the lungs were seen in three females and three males aged 46–69 years, with the

mean age of 58.5 years. In four cases, the right lung was affected, in two patients – the left one. The size of the tumors ranged from one to several cm.

Surgical materials were fixed in formalin and referred to our chair, where sections were prepared, embedded in paraffin and stained with HE, Congo red, and immunohistochemically using the following antibodies: anti- AA amyloid, AL amyloid, transthyretin, beta-2-microglobulin and surfactant A.

Results

From the histological viewpoint, sections collected from pulmonary tumors demonstrated the presence of uniform extracellular hyaline material forming irregular fields. Eosin staining resulted in a pale pink hue of the material. Among amyloid deposits, scattered regions of fibrous tissue with spindle cells and small lymphocyte infiltrations were seen (Fig. 1).

Congo red stained the deposits orange-red; under the polarized light, a part of deposits changed the color to apple green, what resulted from the so-called chromatic polarization (Fig. 2). At times, on the periphery of the lesions and sometimes in deeper layers, there were observed giant, multinucleated cells of the foreign body type (Fig. 3); no such cells were found in Case 6. In addition, the lesions presented with mildly abundant inflammatory infiltration of the chronic type, mostly with lymphocytes. In the case where an amyloid tumor was concomitant with a lymphoma, a striking feature was an intensified presence of the B CD20+ lymphocytes, both at the periphery and within the deposits, their amount being much greater as compared to the other tumors (Fig. 4). Calcifications appearing as small nodules and dust were noted in Cases 1, 3, 5 and 6, ossification only in Case 1, where bone marrow was also present within the bony structures. The amyloid tumors were sharply delineated at the border with the surrounding pulmonary parenchyma, which showed no other pathological lesions.

Five of the presented cases were AL amyloid positive (Fig. 5). In one tumor (Case 2), amyloid deposits were associated with marginal zone lymphoma of the lung (BALT). In Case 3, apart from AL amyloid, trace amounts of transthyretin were found, while Case 6 revealed solely the presence of transthyretin (Fig. 6). AA amyloid was not represented in the tumors (see Table 1).

Also beta-2-microglobulin was found in trace amounts in Case 2 and 3, while traces of surfactant A were seen in Case 1. The entire combination of the latter results may be regarded as problematic and most likely negative (resulting from artifacts).

Discussion

The first reports describing pulmonary amyloidosis were published by Virchow (1857) and Lesser (1877) [cf. 14, 31, 34, 42]. Isolated nodular lesions are most commonly the subject of single communications [17, 19, 26, 33, 40, 43, 44]; rarely only do the investigators present larger series of cases collected over a prolonged period [6, 14, 42]. Since, apart from autopsy findings, often it is impossible to demonstrate that amyloid was deposited solely in the lungs, Hui et al. [14] use the term “amyloidosis presenting in the lower respiratory tract”.

Isolated solid amyloid tumors involving the lungs are very rare and their origin is somewhat shrouded in mystery. They result from various types of pathologic proteins forming deposits in pulmonary parenchyma. Upon diagnosis, such tumors may be static or they may gradually increase in size; a patient may present with a single or multiple lesions [13]. According to Hasleton [12], the tumors are usually sin-

TABLE 1

	No.	Sex	Age	Location	AA	AL	Transthyretin	Beta-2-micro-globulin	SP-A Surfactant A	Concomitant disease
1	1496103	M	58	Right lung	–	+	–	+/–	+/–	
2	1484638, 24837	F	46	Left lung	–	+	–	+/–	–	BALT
3	1318989	M	58	Right lung	–	+	+	–		Amyloidosis of mediastinal lymph nodes
4	1426792	F	63	Right lung	–	+/–	–	–	–	
5	123244	F	69	Left lung	–	+	–	–	–	
6	135888	M	57	Right lung	–	–	+	–	–	

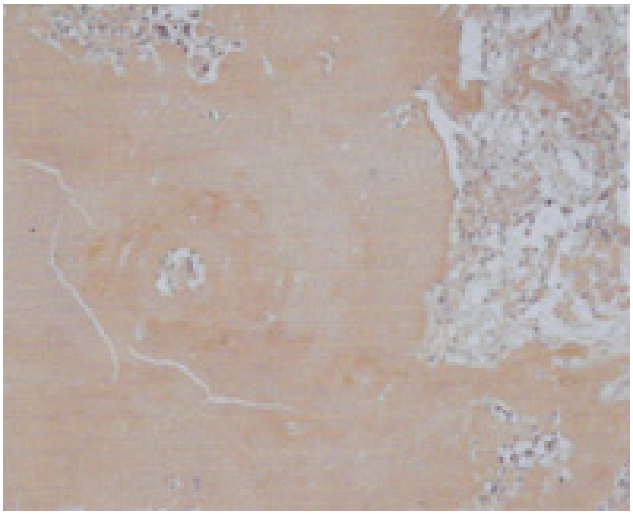

Fig. 1. Congo red stained amyloid deposits in the lung.

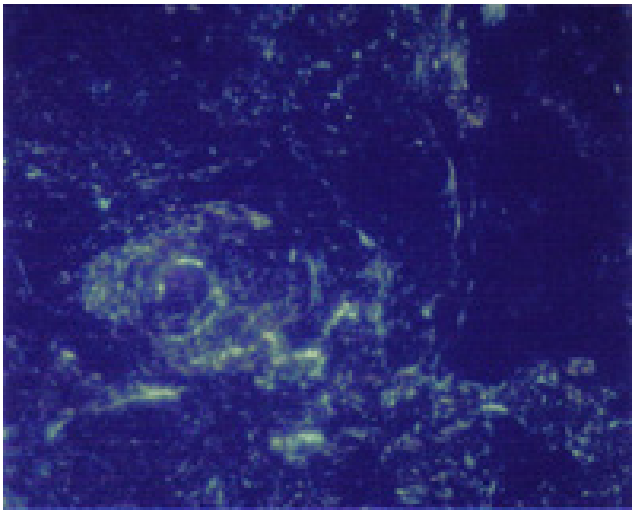

Fig. 2. The same site as in Figure 1 seen under a polarizing microscope. Note the apple-green amyloid polarization.

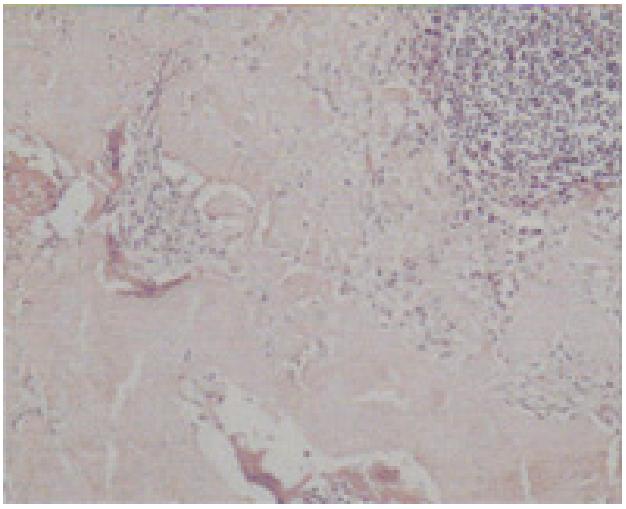

Fig. 3. Giant multinucleated cells of the foreign body type situated on the periphery of the amyloid deposit.

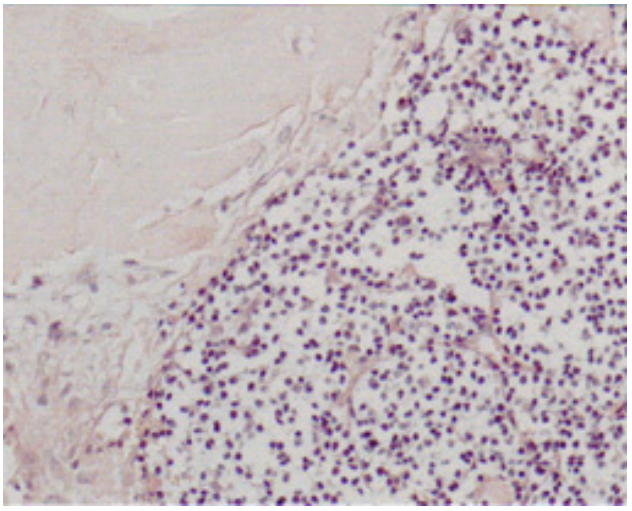

Fig. 4. Numerous lymphocytes from marginal zone situated in the vicinity of amyloid deposits.

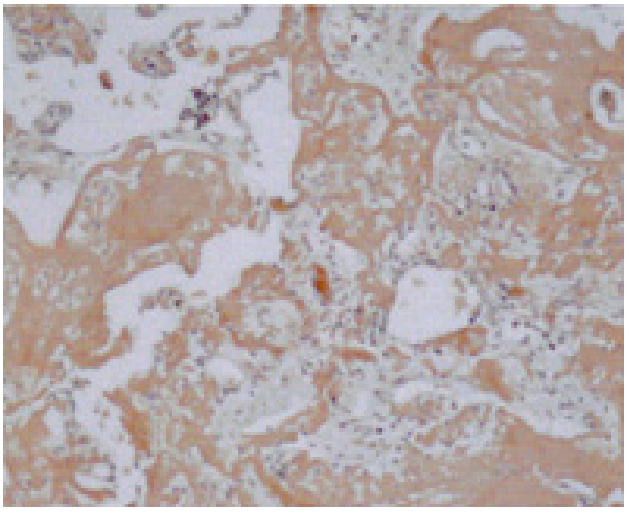

Fig. 5. Positive reaction to immunoglobulin light chains within amyloid deposits.

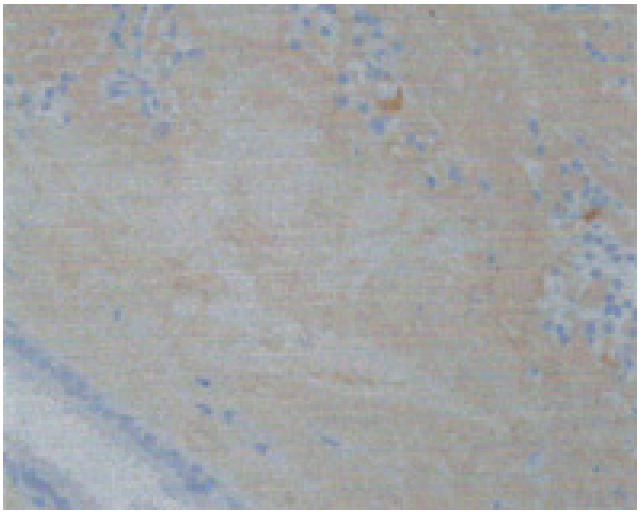

Fig. 6. Weak reaction to transthyretin within amyloid deposits (Case 6).

gle, and in 1/4 of nodular pulmonary amyloidosis cases, they become calcified. In some instances, the lesions demonstrate ossification or chondrometaplasia. Hui et al. [14] estimated the mean age of patients with nodular pulmonary amyloidosis as 64 years of life, what is close to our results. According to these authors, amyloid tumors are equally common in patients of both sexes. Patients with amyloid pulmonary tumors described by other investigators were usually clinically asymptomatic, similarly as in our material, and the only feature of the disease was a pulmonary tumor detected in the course of X-ray examinations [14]. On the other hand, in cases of tracheobronchial amyloidosis or when the stroma is involved, the affected individuals often report dyspnea and other pulmonary complaints [14, 31]. The size of amyloid tumors presented in the series described by Hui et al. [14] ranged from 0.6 to 9 cm, with the mean size of 3 cm. In their 28 cases, the right lung was involved more frequently (2.5 times as often as the left lung), with the lesion occurring in the inferior lobe in 27% of cases.

Senile amyloidosis usually does not appear in the nodular form, although isolated cases of this type have been reported; the disease is rarely seen in patients below 80 years (in less than 2% of affected individuals). In the group of individuals deceased between 80 and 84 years of age, it is encountered in approximately 10%, while among patients who die when more than 85 years old, the disease is manifested in as many as more than 20% of cases. Usually, in those cases there is a mild involvement of blood vessel walls and intra-alveolar septa, with concomitant amyloid tumor-type lesions in the heart [21]. This type of amyloidosis is probably associated with inflammatory processes, immune system abnormalities and genetic factors. Our cases have developed in younger patients and they manifested no morphological features characteristic of senile amyloidosis. According to Strege et al. [39], senile amyloidosis is associated with transthyretin deposit formation.

Over the period of 14 years, at the Mayo Clinic only seven patients with amyloid tumors of the lungs were seen; their mean age was 67 years [42]. The authors did not report, however, the chemical type of the encountered amyloid. At present, the prevailing opinion holds that pulmonary deposits most commonly are formed by AL amyloid in association with immunoglobulin light chains [7, 13, 14, 19, 23, 24, 27, 28, 30, 38]. Hui et al. [14] did not observe, however, monoclonal plasma cells in the vicinity of pulmonary lesions, and they related their presence to the inflammatory reaction developed in association with the amyloid. In 86% of such patients with pulmonary tumors, a monoclonal protein is found in the serum and urine, but its level may be low and it may be missed in tests if no immunofixation method is employed [11, 13]. In our cases, no thorough tests were performed to detect serum and urine monoclonal immunoglobulins. The reasons for their presence may be also sought in chronic inflammatory processes involving the lung. It may result from excessive production of normal or abnormal light chains or else be associated with abnormal function of macrophages, which are responsible for the removal of these chains. The report by Lachmann et al. [22] should be also borne in mind; the authors employed special investigative methods and found out that in approximately 9% of AL amyloidosis cases, immunohistochemical reactions may indicate the presence of this type of amyloid, while in truth the patients may suffer from other amyloidosis forms. In such cases, the positive result is a consequence of errors inherent in the method. A false negative result in the case of AL amyloid may in turn be a consequence of an altered immunoglobulin fragment, what leads to absence of reactivity to the employed antibody [22, 36].

Olsen et al. [29] suggested that in localized amyloidosis, including the pulmonary form, an active role was possibly played by giant multinucleated cells that were involved in amyloid fiber formation through modification of trapped light chain precursor proteins. Also Hui et al. [14] observed an increased incidence of giant cells and plasma cells in nodular amyloidosis as compared to other types of pulmonary disease.

In some cases, pulmonary amyloidosis results from the presence of a neoplastic disease involving the lymphoid tissue, with the lesions situated locally, e.g. lymphoplasmocytic immunocytoma in two patients reported by Ihling et al. [15]. Also Dacic et al. [6], Davis et al. [9] and Lim et al. [25] described cases of a localized amyloid tumor in the lung concomitant with a the pulmonary marginal zone lymphoma. In our material, we also observed such a patient (Case 2). Rostano et al. [35] presented nodular deposits of monoclonal immunoglobulin light chain deposits in the case of B lymphocyte dyscrasia. It seems possible that – apart from obvious cases that occur concomitantly with lymphomas involving the lungs – other AL amyloid tumors may be a result of indolent localized pulmonary lymphomas, whose the primary causes may be sought in chronic inflammatory processes; amyloid tumors may also result from local depositing of amyloid originating from light chains that are present in the serum in excessive amounts. According to Dacic et al. [6], who investigated six cases of amyloid tumors of the lungs without concomitant lymphomas, and five cases accompanied by lymphomas, there is a possibility of differentiating these lesions based on their morphological evaluation. The special lymphocyte arrangement (tracking), infiltrations of the pleura, sheet-like plasma cells clusters and reactive nodules are characteristic of lymphomas. Also in the immunohistochemical investigations carried out by the above authors, such features as the predominance of B

lymphocytes (CD20+, CD79α+), restrictions of light chains and aberrant antigen expression CD20/CD43 were helpful in differentiating these lesions. In our case of marginal zone lymphoma, we noted similar abundant lymphocyte B infiltrations within the tumor and its surroundings.

Transthyretin may be another type of nodular amyloid that is deposited in the lungs; this happens in senile or localized amyloidosis, and sometimes when the disease if familial and genetically determined. Such was the case of a 57-year old male patient from our series (Case 6). A striking feature in this patient was the absence of giant multinucleated cells.

It should be also borne in mind that sometimes negative immunohistochemical reactions to identified amyloid may be caused by amyloid produced by neoplastic cells, most often carcinomas of the lung, what has been observed in patients with tracheobronchial amyloidosis [31].

Johansson et al. [16] demonstrated that in some cases also some surfactant forms might constitute pulmonary amyloid-producing material; this was true for C surfactant. No anti-C surfactant antibody is currently available commercially, and A surfactant was not present in the amyloid deposits.

Nodular pulmonary amyloidosis is treated surgically. Sometimes patients present with recurrent disease, but usually a complete cure is achieved, what proves the localized form of the lesion [14]. Tracheobronchial amyloidosis, associated with bronchial stenosis, may be treated using a laser (YAG laser) and the prognosis is good for patients with AL amyloid deposits, although somewhat poorer in comparison to cases of nodular amyloidosis [13, 31]. Some forms of amyloidosis involving the stroma and associated with lymphomas have been treated using chemotherapy, although the outcome of such treatment is not devoid of ambiguity [13].

References

1. *Celli BR, Rubinow A, Cohen AS, Brody JS:* Patterns of pulmonary involvement in systemic amyloidosis. Chest 1978, 74, 543–547.
2. *Chen KTK:* Amyloidosis presenting in the respiratory tract. In: Pathology Annual Rosen PP, Fechner RE, eds.1989, 253–273.
3. *Colley FV, Carrington ChB:* Pulmonary amyloidosis. In: Pathology of the Lung. Thurlbeck WM, ed. Thieme Med Publ, Stuttgartd, New York 1988, 489–493.
4. *Cordier JF, Loire R, Brune J:* Amyloidosis of the lower respiratory tract. Clinical and pathologic features in a series of 21 patients. Chest 1986, 90, 827-831.
5. *Corrin B:* Pathology of the Lungs. Churchill Livingstone, London 2000, 585–587.
6. *Dacic S, Colby ThV, Yousem SA:* Nodular amyloidoma and primary pulmonary lymphoma with amyloid production: a differential diagnostic problem. Modern Pathol 2000, 13, 934–940.
7. *Da Costa P, Corrin B:* Amyloidosis localized to the lower respiratory tract: probable immunoamyloid nature of the tracheobronchial and nodular pulmonary forms. Histopathology 1985, 9, 703–710.
8. *Dail DH:* Metabolic and others disease. In: Pulmonary Pathology. Dail DH, Hammar SP, eds. Springer Verlag, New York 1994, 713–720.
9. *Davis CJ, Butchart EG, Gibbs AR:* Nodular pulmonary amyloidosis occurring in association with pulmonary lymphoma. Thorax 1991, 46, 217–218.
10. *Dundore PA, Aisner SC, Templeton PA et al:* Nodular pulmonary amyloidosis: diagnosis by fine-needle aspiration cytology and review of the literature. Diag Cythopathol 1993, 9, 562–564.
11. *Gertz MA, Kyle RA:* Primary systemic amyloidosis. A diagnostic primer. Mayo Clin Proc 1989, 64, 1505–1519.
12. *Hasleton PS:* Spencer's Pathology of the Lung. McGraw-Hill, New York 1996, 776–781.
13. *Howard ME, Ireton J, Daniels F et al:* Pulmonary presentation of amyloidosis. Respirology 2001, 6, 61–64.
14. *Hui AN, Koss MN, Hohcholzer L et al:* Amyloidosis presenting in the lower respiratory tract. Arch Pathol Lab Med 1986, 110, 212–218.
15. *Ihling C, Weirich G, Gaa A, Schaefer HE:* Amyloid tumors of the lung – an immunocytoma. Path Res Pract 1996, 192, 446–452.
16. *Johansson J:* Membrane properties and amyloid fibril formation of lung surfactant protein C. Biochem Soc Trans 2001, 29, 601–606.
17. *Kamiński Z, Utnik A:* Odosobniona amyloidoza płuc – postać guzkowa. Pneum Pol 1976, 44, 1049-1056.
18. *Katzenstein AA:* Katzenstein and Askin Surgical Pathology of non-Neoplastic Lung Diseases. Saunders Comp, Philadelphia 1997, 174–177.
19. *Khoor A, Myers JL, Tazelaar HD, Kurtin PJ:* Amyloid-like pulmonary nodules, including localized light-chain deposition: clinicopathologic analysis of three cases. Am J Clin Pathol 2004, 121, 200–204.
20. *Kobayashi H, Matsuoka R, Kitamura S et al:* Sjögren's syndrome with multiple bullae and pulmonary nodular amyloidosis. Chest 1988, 94, 438–440.
21. *Kunze WP:* Senile pulmonary amyloidosis. Path Res Pract 1979, 164, 413–422.
22. *Lachmann HJ, Booth DR, Booth SE et al:* Misdiagnosis of hereditary amyloidosis as AL (primary) amyloidosis. N Engl J Med 2002, 346, 1786–1791.
23. *Laden SA, Harley RA:* Amyloid: a pictorial study highlighting the nodular pulmonary form. Lab Invest 1982, 46, 47A–48A.
24. *Laden SA, Cohen MI, Harley RA:* Nodular pulmonary amyloidosis with extrapulmonary involvement. Hum Pathol 1984, 15, 594–597.
25. *Lim JK, Lacy MQ, Kurtin PJ et al:* Pulmonary marginal zone lymphoma of MALT type as a cause of localised pulmonary amyloidosis. J Clin Pathol 2001, 54, 642–646.
26. *Matsumoto K, Ueno M, Matsuo Y et al:* Primary solitary amyloidoma of the lung: findings of CT and MRI. Eur Radiol 1997, 7, 586–588.
27. *Michaels L, Hyams VJ:* Amyloid in localised deposits and plasmocytomas of the respiratory tract. J Pathol 1979, 128, 29–38.
28. *Miura K, Shirasawa H:* Lambda III subgroup immunoglobulin light chains are precursor protein of nodular pulmonary amyloidosis. Am J Clin Pathol 1993, 100, 561–566.
29. *Olsen KE, Sletten K, Sandgren O et al:* What is the role of giant cells in AL-amyloidosis. Amyloid 1999, 6, 89–97.
30. *Page DL, Iisersky C, Harada M et al:* Immunoglobulin origin of localized nodular pulmonary amyloidosis. Resp Exp Med 1972, 159, 75–86.
31. *Papla B, Dubiel-Bigaj M:* Tracheobronchial amyloidosis. Pol J Pathol 1998, 49, 27–34.
32. *Papla B, Rudnicka L:* Primary amyloid tumors of the lung. XVI Congress of the Polish Society of Pathologists, IX 2004, Wrocław. Pol J Pathol 2004, 55(Suppl), 39(abs).
33. *Podbielski FJ, Nelson DG, Pearsall GF et al:* Nodular pulmonary amyloidosis. J Thorac Cardiovasc Surg 1997, 114, 289–291.

34. *Remiszewki P, Langfort R, Orłowski TM et al:* Pulmonary amyloidosis – own experience. Pneumonol Alerg Pol 2001, 69, 655–662.
35. *Rostagno A, Frizzera G, Ylagan L et al:* Tumoral non-amyloidotic monoclonal immunoglobulin light chain deposits ("aggregoma") presenting feature of B-cell dyscrasia in three cases with immunohistochemical and biochemical analyses. Br J Haematol 2002, 119, 62–69.
36. *Rocken CH, Sletten K:* Amyloid in surgical pathology. Virchows Arch 2003, 443, 3–16.
37. *Rubinow A, Celli BR, Cohen AS et al:* Localized amyloidosis of the lower respiratory tract. Am Rev Respir Dis 1978, 118, 603–611.
38. *Stokes MB, Jagirdar J, Burchstin O et al:* Nodular pulmonary immunoglobulin light chain deposits with coexistent amyloid and nonamyloid features in an HIV-infected patient. Mod Pathol 1997, 10, 1059–1065.
39. *Strege RJ, Saeger W, Linke RP:* Diagnosis and immunohistochemical classification of systemic amyloidoses. Virchows Arch 1998, 433, 19–27.
40. *Sybilski Z:* Przypadek odosobnionej skrobiawicy płuca wyleczony operacyjnie. Pneum Pol 1977, 45, 499–450.
41. *Thompson PJ, Citron KM:* Amyloid of the lower respiratory tract. Thorax 1983, 38, 84–87.
42. *Utz JP, Swensen SJ, Gertz MA:* Pulmonary amyloidosis. The Mayo Clinic experience from 1980-1993. Ann Intern Med 1996, 124, 407–413.
43. *Thompson PJ, Jewkens J, Corrin P et al:* Primary bronchopulmonary amyloid tumour with massive hilar lymphadenopathy. Thorax 1983, 38, 153–154.
44. *Yoshino I, Katsuda Y, Yokoyama H et al:* Solitary amyloid nodule in the lung. Scand Cardiovasc J 1997, 31, 121–122.

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