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CASE REPORT / ПРИКАЗ БОЛЕСНИКА

Nodular amyloidosis of the lung presenting as lung malignancy

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SUMMARY

Introduction Amyloidosis is a disease associated with the extracellular deposition of insoluble protein material called amyloid. It can be acquired or hereditary, systemic or organ-limited. Nodular pulmonary amyloidosis is defined as one or more tumefactive amyloid deposits in the lungs.

Outlines of cases This study presents two cases that were hospitalized at the Institute for Pulmonary Diseases to clarify the origin of lesions detected on computed tomography (CT) scans of lung parenchyma. In the first case, in a 78-year-old woman, numerous non-calcified nodules were described on the chest CT. The patient died during hospitalization, and the autopsy revealed diffusely distributed greyish-yellow nodular lesions in the upper and middle parts of the right lung, as well as lesions in the form of partially calcified nodules in both lungs. Histological analysis of samples from macroscopically described nodules confirmed nodular amyloidosis. The second patient is male, 58 years old, who was operated on for rectal adenocarcinoma three years ago. A CT scan of the lung parenchyma shows a tumor nodule localized in the lower lobe and a nodular lesion localized in the upper lobe of the right lung. Histological analysis confirmed that the lesion from the lower lobe corresponds to the metastasis of colorectal cancer, while in the lesion from the upper lobe amyloid deposits were found.

Conclusion Pulmonary nodular amyloidosis is a rare condition, and because of the imaging similarities it is difficult to distinguish it from malignant nodules in the lung parenchyma. Therefore, as a part of routine practice, a definitive diagnosis of amyloidosis needs to be confirmed by tissue biopsy.

Keywords: amyloidosis; amyloid; lung malignancy; autopsy; Congo red

INTRODUCTION

Amyloidosis is a disease associated with the extracellular deposition of insoluble protein material called amyloid in various tissues and organs. This condition can be found in humans as well as in other vertebrates. The term amyloid was used in medicine for the first time by Rudolf Virchow in 1854. Amyloid deposits are composed of fibril proteins (95%), and the remaining part is amyloid P and glycoproteins. Up to now, 36 amyloid fibril proteins and their precursors have been identified in humans, and ten in other vertebrates [1, 2].

Amyloidosis can be acquired or hereditary, systemic or organ-limited. Pulmonary amyloidosis can be seen in three distinct forms: diffuse alveolar-septal amyloidosis, nodular pulmonary amyloidosis, and tracheobronchial amyloidosis [3].

Nodular pulmonary amyloidosis is defined as one or more tumefactive amyloid deposits in the lungs and usually represents incidental findings on chest imaging [4]. The imaging similarities of multiple pulmonary nodules (with calcification and cavitation) with malignant lung tumors make differential diagnosis particularly difficult. For that reason, histological confirmation should be mandatory. In this case study, we report two cases of pulmonary nodular amyloidosis that were suspected of lung malignancy.

Case No. 1

A 78-year-old woman was admitted to the Institute for Pulmonary Diseases of Vojvodina for cough, fever, hemoptysis and nausea. Upon admittance, at initial examination, there was not any palpable lymphadenopathy. Results of periphery blood showed anemia and discrete leukocytosis, while the analysis of bio-humoral tests showed elevated values of inflammatory markers such as urea and lactate dehydrogenase. In addition, a blood gas test showed hypercapnic respiratory failure.

Computed tomography (CT) scan of the chest has shown multiple non-calcified nodules in the right lung (between segments S2/S6 measuring 30 × 50 mm and S5 38 × 12 mm), and in the upper lobes of both lungs, and in the lower lobe of the left lung there were partly calcified nodules with a diameter of up to 24 mm. Cytological analysis showed that tracheobronchial aspirate contained mucopurulent exudates.

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Despite the treatment, intensive monitoring, and care, on day 12 of hospitalization the patient died. At the autopsy, the weight of the left lung was 670 g, while the weight of the right lung was 990 g. Both lungs were pinkish-colored on the cross-section, and a large amount of pale pink foamy fluid flew from its cut surface. In the upper and middle lobes of the right lung and the upper lobe of the left lung, individual nodules of greyish-yellow color, less than 2 cm in diameter were found. In the lower lobes on both sides of the lungs, there were greyish-yellow nodules, up to 4.6 cm in diameter (Figure 1). Some of them had the appearance of grapes.

Histologically, nodules are composed of homogeneous, densely eosinophilic amorphous material. Deposits are orange-red on Congo red stain (Figure 2) and under polarized light show apple-green birefringence (Figure 2). In the surrounding lung tissue, during the pathohistological examination, hemorrhagic infarcts, chronic catarrhal bronchitis, emphysema, and pulmonary edema (which was established as the cause of death) were revealed. Elements of malignant tissue were not seen.

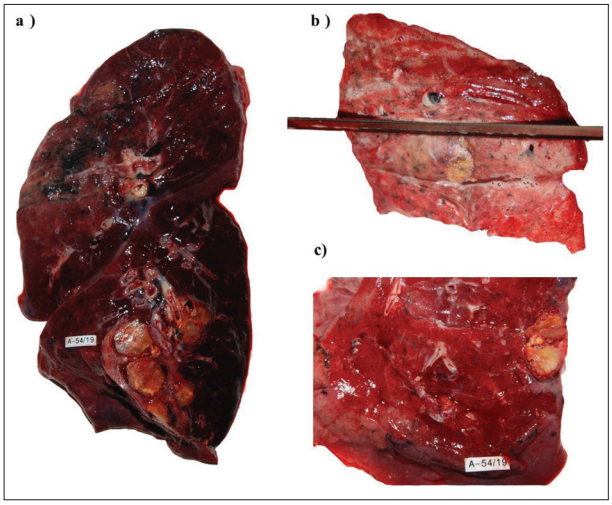

Figure 1. Gross images of lung with amyloid nodules

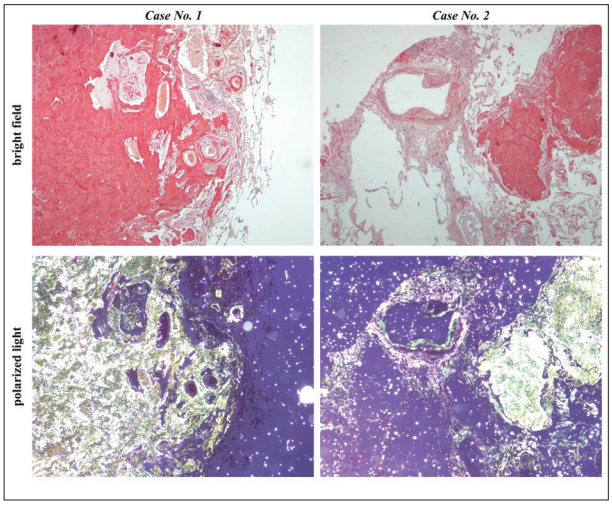

Figure 2. Congo red stained lung parenchyma with amyloid deposit, examined under bright field and polarized light microscopy, 4 ×

Case No. 2

A 58-year-old male patient was admitted to the Institute for Pulmonary Diseases of Vojvodina for identification of etiology of pathologic lesions in lung parenchyma which were found on CT imaging. His past medical history included arterial hypertension and dilated cardiomyopathy, and three years ago, the patient was diagnosed with adenocarcinoma of the rectum, which had been surgically removed.

During the surgery, whitish lesions were noted in the upper lobe of a lung. Tissue fragments from the lower and upper lobe of the right lung were sent for histopathological analysis.

Upon gross examination of lung parenchyma of the lower lobe of the lung, we found a clearly defined whitish tumor nodule, with 3.7 × 3 cm in size. In tissue samples taken from that area, we found a tumor tissue that, due to histological characteristics, corresponds to the metastasis of colorectal cancer.

In the histological samples from the upper lobe of the right lung in alveolar parenchyma there were nodular acellular homogeneous deposits that were eosinophilic by standard histological staining. Around described deposits, a lymphocyte infiltrate as well as giant cells were noted. Upon Congo red histochemical staining, acellular deposits were colored orange, and under polarized light showed apple-green birefringence (Figure 2). Described findings correspond to nodular amyloidosis.

The study was approved by the Ethics Committee of the Institute for Pulmonary Diseases of Vojvodina.

DISCUSSION

Amyloidosis is a rare disease of unclear etiology, and its most common clinical forms are amyloid A amyloidosis, immunoglobulin light chain amyloidosis, transthyretin amyloidosis, and beta-2 microglobulin amyloidosis (Aβ2M) [5, 6].

The exact incidence of amyloidosis is unknown, but estimates show that 6–10 cases per million are diagnosed annually [7]. Amyloid deposits commonly affect males (2:1) of the middle age group (50–60 years) [8].

Amyloid can even affect pleura, pulmonary arteries, lymph nodes, and diaphragm [9, 10]. Deposition of amyloid results in destruction of tissue structure and impairment of organ function. The diagnosis of amyloidosis can only be confirmed by the histopathologic section of tissue stained with Congo Red, and the amyloid will show green apple birefringence under polarized light, as in this case. In addition, amyloid can be detected when stained with metachromatic dye, such as crystal violet, or with thioflavin T as a fluorescent marker [11, 12].

Nowadays, the use of immunohistochemistry in combination with clinical testing can help identify precursor proteins in amyloid deposits and their subtyping [13, 14].

Mass spectrometry-based proteomic analysis can be performed on formalin-fixed, paraffin-embedded tissue,

and due to its high sensitivity and specificity, this method can be applied in clinical biopsy specimens and it will be a useful tool in amyloid subtyping [5].

Clinically, nodular pulmonary amyloidosis is asymptomatic and on CT is seen as multiple nodules of varying size with sharp or lobulated margins, usually peripherally located in lower lobes of the lungs [4, 15]. Calcifications are seen in 50% of cases, and one of the characteristics is slow nodule growth with no regression [16, 17]. That is very similar to localization of deposits in our first case, where we had amyloid nodules in lower lobes of both lungs, but the uncommon presentation was finding amyloid deposits in the middle lobe of the right lung.

For pulmonary nodular amyloidosis, differential diagnosis includes malignancy of the lung (primary or metastatic) and granulomatous diseases [18]. Previous study reported that during fludeoxyglucose (18F-FDG) positron emission tomography (PET)/CT imaging of patients with amyloid deposits, most of them showed increased FDG uptake, but no FDG uptake has been mentioned [19]. Therefore, 18F-FDG PET/CT is not a useful diagnostic tool for distinguishing amyloidosis from lung malignancy, but in the future, the use of some more specific tracers such as C-labeled Pittsburgh compound B and 18F-florbetapir might be a better solution [20].

Pathohistological examination is essential for a definitive diagnosis. Differential diagnoses of nodular pulmonary amyloidosis on histological tissue specimens include pulmonary hyalinizing granuloma and amyloid-like nodules in light-chain deposition disease. In light-chain deposition disease, amyloid-like nodules in lung parenchyma are histologically very similar to amyloid. However, they are composed of κ-light chain fragments which are Congo red negative and do not form fibrils, but present as granular material under electron microscope [5].

Pulmonary hyalinizing granuloma is a rare benign disease, and on chest imaging, shows unilateral or bilateral well-defined nodules. In histological slides, hyalinizing granulomas are different from amyloid deposits. They are presented as fibrotic nodules composed of hyalinized collagen bundles with lamellar arrangement, so they are not homogeneous and the Congo red staining is negative [21]. Chronic inflammation is localized both around and within them. The inflammatory infiltrate predominantly contains lymphocytes and plasma cells, but it can also hold neutrophils and histiocytes [22].

Studies have shown that most cases of nodular pulmonary amyloidosis are associated with B-cell lymphomas [23] and mucosa-associated lymphoid tissue lymphoma [24], and association with pulmonary amyloidosis and lymphomas has been found in Sjögren's disease [25, 26, 27]. In the second case, we reported nodular amyloidosis in a patient with metastatic adenocarcinoma in the same lung.

Pulmonary nodular amyloidosis is a rare condition, but because of imaging similarities it is difficult to distinguish it from malignant nodules in the lung parenchyma. For that reason, it should be added to the differential diagnosis. In routine practice, a definitive diagnosis of amyloidosis needs to be confirmed by tissue biopsy and, in addition to standard H & E staining, histochemical Congo red should be used.

Conflicts of interest: None declared.

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Нодуларна амилоидоза плућа представљена као малигни тумор плућа

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САЖЕТАК

Увод Амилоидоза је болест повезана са ванћелијским таложењем нерастворљивог протеинског материјала који се назива амилоид. Обољење може бити стечено или наследно, системско или ограничено на органе. Нодуларна плућна амилоидоза се дефинише као један или више тумефактивних депозита амилоида у плућном паренхиму.

Прикази болесника У овој студији приказана су два болесника која су хоспитализована на Институту за плућне болести како би се разјаснило порекло патолошких промена у плућном паренхиму детектованих на снимцима компјутеризоване томографије. У првом описаном случају код особе женског пола, старости 78 година, на компјутеризованој томографији грудног коша описују се бројни некалцификовани нодуси, међутим током хоспитализације дошло је до леталног исхода. На аутопсији се на плућима уочавају сивкасто-жућкасте нодуларне промене дифузно распоређене у горњим и средњим партијама десног плућног крила, као и промене у виду делимично калцификованих чворића локализованих у оба плућна крила. Хистолошком анализом узорака из макроскопски описаних нодуса доказана је нодуларна амилоидоза.

Болесник из другог приказаног случаја је мушког пола, старости 58 година, који је три године раније оперисао аденокарцином ректума. На компјутеризованој томографији плућног паренхима описује се туморски нодус који је локализован у доњем делу десног плућног крила, као и нодулирана промена локализована у горњем режњу десног плућног крила. Хистолошком анализом постоперативних узорака утврђено је да нодус из доњег режња одговара метастази колоректалног карцинома, док се у узорку из горњег режња десног плућног крила налазе депозити амилоида.

Закључак Плућна нодуларна амилоидоза је ретко стање, а због сличности на дијагностичком имиџингу тешко ју је разликовати од малигних тумора плућа, па у рутинском раду коначна дијагноза амилоидозе мора бити потврђена биопсијом ткива.

Кључне речи: амилоидоза; амилоид; плућни малигнитети; аутопсија; конго црвено