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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 plasmacytomas 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-

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**TABLE 1**

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Location</th>
<th>AA</th>
<th>AL</th>
<th>Transthyretin</th>
<th>Beta-2-microglobulin</th>
<th>SP-A Surfactant A</th>
<th>Concomitant disease</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>58</td>
<td>Right lung</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+/-</td>
<td>+/-</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>46</td>
<td>Left lung</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+/-</td>
<td>–</td>
<td>BALT</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>58</td>
<td>Right lung</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>Amyloidosis of mediastinal lymph nodes</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>63</td>
<td>Right lung</td>
<td>–</td>
<td>+/-</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tr>
<tr>
<td>5</td>
<td>F</td>
<td>69</td>
<td>Left lung</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>57</td>
<td>Right lung</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
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</tr>
</tbody>
</table>
Amyloid deposits in the lungs

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]. 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 is 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


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