Amyloid-like Pulmonary Nodules, Including Localized Light-Chain Deposition

Clinicopathologic Analysis of Three Cases

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Abstract

Amyloid-like pulmonary nodules have been described in patients with systemic light-chain deposition disease, but their significance in other clinical contexts is unknown. We examined biopsy specimens of amyloid-like pulmonary nodules from 3 women without systemic light-chain deposition disease. Patient 1 (aged 62 years) had multiple pulmonary nodules and underwent 2 separate lung biopsies, the first showing nodules composed of κ light-chain deposits accompanied by low-grade lymphoplasmacytic lymphoma limited to the lung and the second, obtained after chemotherapy 9 months later, showing only residual nodules without persistent lymphoma. Patients 2 (aged 65 years) and 3 (aged 69 years) had asymptomatic solitary pulmonary nodules. In all cases, electron microscopic examination showed dense granular extracellular deposits without the fibrillary characteristics of amyloid. Amyloid-like nodules should be distinguished from nodular amyloidosis and, in some patients, might represent a localized form of light-chain deposition.

Amyloid is a form of fibrillar protein that is deposited in the extracellular matrix and has characteristic physical, ultrastructural, immunophenotypic, and tinctorial properties.1 Pulmonary amyloidosis can take a variety of forms and traditionally is separated into nodular, tracheobronchial, and diffuse alveolar septal forms.2 Nodular pulmonary amyloidosis comprises single or multiple nodules characterized by central amyloid deposition associated with a minor inflammatory infiltrate of lymphocytes, plasma cells, and multinucleated histiocytes. Patients usually are asymptomatic and have no underlying systemic disease. The prognosis is excellent. Occasional reports have described amyloid-like nodules in which the eosinophilic proteinaceous deposits lack histochemical, immunophenotypic, and ultrastructural features of amyloid.3-5 Amyloid-like pulmonary nodules have been described in patients with systemic light-chain deposition disease (LCDD),6 but the significance of amyloid-like nodules in other clinical contexts is unknown. We describe amyloid-like nodules in 3 patients without systemic LCDD.

Materials and Methods

We searched the surgical pathology files of Mayo Clinic, Rochester, MN, and our own consultation files to identify patients with the diagnosis of “amyloid-like nodules.” All available slides from pathologic examination of tissue from patients identified as having amyloid-like nodules were reviewed. Paraffin section immunoperoxidase staining was performed in all cases by using a standard peroxidase-antiperoxidase technique [Table I]. Slides used for serum amyloid A and P proteins were first deparaffinized and then...
pretreated with 44% formic acid and rinsed in cool water. Tissue was retrieved from all paraffin blocks and processed in a standard manner for ultrastructural studies.

Clinical information was obtained from medical records, pathology reports, and contributing pathologists.

Results

Clinical Findings

Three cases (all patients were women) with amyloid-like nodules were identified. The clinical findings are summarized in Table 2.

Case 1

The patient (aged 62 years) was referred to Mayo Clinic for evaluation of multiple, bilateral pulmonary nodules discovered during an episode of severe exacerbation of asthma. She also reported a 20-pound weight loss and night sweats occurring for several weeks. Laboratory evaluation revealed no serum or urine paraprotein. The serum creatinine concentration was normal. Thoracotomy and right middle-lobe biopsy demonstrated lymphoplasmacytic lymphoma. Staging studies revealed no evidence of extrapulmonary disease. She was treated with chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone [modified CHOP]), but the pulmonary nodules persisted. Nine months after the first lung biopsy, she underwent video-assisted thoracoscopic wedge biopsy of the left lower lobe. She was followed up without additional chemotherapy for 1 year after the second lung biopsy. The pulmonary nodules were stable. She had no evidence of systemic lymphoma or paraproteinemia, and she had normal renal function.

Cases 2 and 3

In case 2, the patient (aged 65 years) had an asymptomatic solitary pulmonary nodule in the right upper lobe. In case 3, the patient (aged 69 years) had an asymptomatic solitary pulmonary nodule in the left upper lobe. Both patients underwent lobectomy elsewhere for suspected neoplasms. Neither had evidence of systemic disease, an associated lymphoproliferative disease, or a plasmacytic disorder.

Pathologic Findings

The first biopsy specimen in case 1 showed 2 nodules, one measuring 1.5 cm and the other 5.0 cm in greatest dimension. The second biopsy specimen in this case,

Table 1

Immunohistochemical Antibody Panel Used to Examine Amyloid-Like Pulmonary Nodules

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Clonality</th>
<th>Dilution</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>κ light chain</td>
<td>Polyclonal</td>
<td>1:2,000</td>
<td>DAKO, Carpinteria, CA</td>
</tr>
<tr>
<td>λ light chain</td>
<td>Polyclonal</td>
<td>1:2,000</td>
<td>DAKO</td>
</tr>
<tr>
<td>Serum amyloid P</td>
<td>Polyclonal</td>
<td>1:400</td>
<td>Calbiochem, San Diego, CA</td>
</tr>
<tr>
<td>Serum amyloid A</td>
<td>Clone MC-1</td>
<td>1:50</td>
<td>DAKO</td>
</tr>
</tbody>
</table>

Table 2

Reported Cases of Amyloid-Like Pulmonary Nodules

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/Age (y)</th>
<th>Underlying Condition</th>
<th>Deposit</th>
<th>Pulmonary Manifestation</th>
<th>Extrapulmonary Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>F/62</td>
<td>Low-grade lymphoplasmacytic lymphoma</td>
<td>Nonamyloid κ light chain</td>
<td>Bilateral nodules</td>
<td>No</td>
</tr>
<tr>
<td>Case 2</td>
<td>F/65</td>
<td>None</td>
<td>Nonamyloid, nonimmunoglobulin substance</td>
<td>Solitary nodule (right upper lobe)</td>
<td>No</td>
</tr>
<tr>
<td>Case 3</td>
<td>F/69</td>
<td>None</td>
<td>Nonamyloid, nonimmunoglobulin substance</td>
<td>Solitary nodule (left upper lobe)</td>
<td>No</td>
</tr>
<tr>
<td>Kijner and Youssef</td>
<td>M/59</td>
<td>Systemic light-chain deposition disease</td>
<td>Nonamyloid κ light chain</td>
<td>Bilateral nodules</td>
<td>Systemic disease with involvement of kidneys</td>
</tr>
<tr>
<td>Morinaga et al</td>
<td>F/54</td>
<td>Extramedullary plasmacytoma of the lung</td>
<td>Nonamyloid κ light chain</td>
<td>Main lesion in left lower lobe with satellite nodules in regional lymph nodes and pleura</td>
<td>No</td>
</tr>
<tr>
<td>Piard et al</td>
<td>M/70</td>
<td>Extramedullary plasmacytoma of the lung</td>
<td>Nonamyloid κ light chain</td>
<td>Solitary nodule (left lower lobe)</td>
<td>No</td>
</tr>
<tr>
<td>Stokes et al</td>
<td>F/44</td>
<td>HIV infection</td>
<td>Amyloid and nonamyloid polyclonal light chains</td>
<td>Bilateral nodules</td>
<td>No</td>
</tr>
</tbody>
</table>
obtained after chemotherapy for lymphoma, contained 5 nodules ranging in size from 0.7 to 2.0 cm in greatest dimension. The resected solitary nodule in case 2 measured 2.4 cm ➥ Image 1, and the one in case 3 measured 4.0 cm in greatest dimension. In all cases, the nodules were well circumscribed with a waxy, pale, tan-gray cut surface.

At low magnification, all nodules were similar and demonstrated extensive paucicellular eosinophilic deposits ➥ Image 2A. At higher magnification, the eosinophilic material was distributed in thick and thin hyalinized bundles in a lamellar arrangement ➥ Image 2B. The hyalinized bundles showed a concentric arrangement around small blood vessels. Occasional clusters of mononuclear cells that included focally abundant plasma cells and a minor background population of small lymphocytes separated the eosinophilic deposits. Multinucleated histiocytes were scattered throughout the lesions. No calcification or ossification was observed. In the first biopsy specimen from case 1, a lymphocytic infiltrate was located away from the eosinophilic deposits and distributed along bronchovascular bundles and interlobular septa.

Multiple stains for amyloid, including Congo red, sulfated alcian blue, thioflavine S, and thioflavine T, were negative in all cases. In addition, paraffin section immunostains were negative for serum amyloid P component and serum amyloid A component. Immunoperoxidase studies performed on both biopsy specimens in case 1 demonstrated immunoreactivity for κ immunoglobulin light chain within the amyloid-like substances and in mature plasma cells and plasmacytoid lymphocytes. Immunostaining performed on paraffin sections of the nodules resected in cases 2 and 3 showed a polyclonal pattern of immunoreactivity for light chains in mature plasma cells. No staining was observed within the eosinophilic amyloid-like material.

The results of ultrastructural studies were similar in all cases and showed poorly preserved tissue characterized by dense granular osmiophilic deposits within the extracellular matrix ➥ Image 3, admixed with haphazardly arranged collagen bundles. No fibrillar deposits typical of amyloid were present.
Discussion

We report 3 cases in which deposits of amorphous, densely eosinophilic material formed nodular masses indistinguishable from nodular amyloidosis on routine sections. Despite the light-microscopic appearance, multiple histochemical and immunohistochemical stains and ultrastructural studies showed no amyloid properties. In 1 case, the nodules were multiple and represented a form of localized nonamyloid light-chain deposition, whereas in the other 2 cases, the nature of the deposits remains unknown.

Amyloidosis may involve the lung in tracheobronchial, diffuse, and nodular forms. In all 3 forms, amyloid classically shows apple-green birefringence when examined under polarized light after staining with Congo red and stains metachromatically (pink) with crystal violet. Staining with thioflavine T and S yields secondary fluorescence when viewed with UV light. Immunoreactivity for amyloid P component is seen in all forms of amyloidosis. Electron microscopic examination characteristically shows a haphazard array of fine, nonbranching, beaded fibrils, ranging from 7.5 to 10 nm in width. Diffuse alveolar septal amyloidosis usually occurs in patients with primary systemic amyloidosis and has a poor prognosis, whereas the tracheobronchial and nodular forms usually are localized to the respiratory tract without evidence of systemic disease. Nodular amyloidosis usually is associated with amyloid light chain, which is in almost all cases. Occasional cases are negative for routine amyloid stains and can be separated from nonamyloid light-chain deposits only by immunohistochemical analysis or electron microscopic examination.

Aside from nodular pulmonary amyloidosis, the histopathologic differential diagnosis for pulmonary amyloid-like nodules includes pulmonary hyalizing granuloma and infectious granulomas. Pulmonary hyalizing granuloma is a rare condition that usually manifests as multiple bilateral lung nodules in young or middle-aged adults. In many patients, hyalizing granulomas are thought to represent an abnormal immunologic reaction to infection, particularly histoplasmosis. Histologically, the nodules of hyalizing granuloma show a lamellar arrangement of thick acellular collagen bundles associated with a peripheral infiltrate of mononuclear cells. The collagen bundles lack the tinctorial and immunohistochemical properties of amyloid. The characteristics of infectious granulomas overlap with those of pulmonary hyalizing granuloma, but the entities may be distinguished if central necrosis is present or organisms are shown by using special stains.

LCDD is a rare clinicopathologic entity characterized by tissue deposition of nonamyloid immunoglobulin light chains. It affects middle-aged patients ranging in age from 35 to 76 years, with a mean of 56 years. The condition affects men 2.5 times more often than women. Most patients have an underlying plasma cell dyscrasia with excessive levels of monoclonal light chains in the serum and urine. Overt multiple myeloma is found in approximately two thirds of cases. Association with other B-cell neoplasms (lymphoma, Waldenström macroglobulinemia, and chronic lymphocytic leukemia) also has been reported.

The clinical manifestations of LCDD are related to the underlying condition and the location of deposits. Renal involvement is present consistently and is characterized by proteinuria, microscopic hematuria, and progressive renal failure. Pulmonary involvement has been detailed in only a few patients. Kijner and Yousem described a patient with LCDD who had dyspnea and bilateral pulmonary nodules but subsequently developed systemic disease with renal failure and died 3 months later (Table 2). Because of the common association with multiple myeloma and systemic involvement, LCDD usually has a grim prognosis.

The main histologic abnormality in LCDD is the presence of eosinophilic extracellular deposits that closely mimic the appearance of amyloid. The results of histochemical stains for amyloid are consistently negative, as are the results of immunohistochemical stains for various amyloid-related proteins such as amyloid P component. In 80% of patients, the deposits are derived from κ immunoglobulin light chain. Ultrastructural studies show dense, granular, extracellular deposits identical to those seen in our cases.

Our patient with primary pulmonary lymphoma also had characteristics of LCDD, but the light-chain deposits seemed to be confined to the lungs. Combination chemotherapy had little effect on the lung disease. At the most recent follow-up,
she had no evidence of a systemic illness and renal function remained unimpaired.

Morinaga and colleagues described similar deposits of nonamyloid light chain in a patient with an extramedullary plasmacytoma involving the left lower lobe of the lung associated with multiple lymph node and pleural nodules interpreted as metastases. Bone marrow biopsies and skeletal surveys revealed no evidence of extrathoracic disease, although—unlike our case—their patient had a persistent serum paraprotein 6 months after surgery. Renal function was normal. More recently, Piard and colleagues described a similar case in which the patient had a solitary pulmonary plasmacytoma associated with deposits of nonamyloid κ immunoglobulin light chain located within and away from the tumor. There was no associated paraprotein or evidence of systemic disease, and the patient remained well 1 year after lobectomy. Our cases with solitary lesions showed no evidence of light-chain deposition on immunohistochemical examination or of lymphoma or plasma cell dyscrasia.

Stokes and colleagues reported clinicopathologic findings in a drug user who was infected with HIV and had multinodular pulmonary immunoglobulin light-chain deposits. As in our patient with primary pulmonary lymphoma, the nodules were bilateral and limited to the lungs. However, in their patient, the deposits had a unique histochemical and ultrastructural profile, with intermixed Congo red–positive fibrillar amyloid and Congo red–negative granular nonamyloid components. Immunohistochemical and immunoelectron microscopic studies showed reactivity of both the fibrillar and granular deposits for κ and λ light chains. The relationship among amyloid-like pulmonary nodules, infection with HIV, and illicit drug use is unknown but did not have a role in any of our cases.

In the 3 cases we report, the patients had pulmonary nodules that resembled nodular amyloidosis but lacked the histochemical, immunohistochemical, and ultrastructural features of amyloid. In patients with low-grade lymphomas or plasmacytomas, amyloid-like nodules can develop as a manifestation of localized light-chain deposition without evidence of systemic disease. Amyloid-like nodules that lack clinical and immunohistochemical evidence of light-chain deposition are of uncertain histogenesis and remain unexplained.

References