

## LOCALIZED TRACHEAL AMYLOIDOSIS

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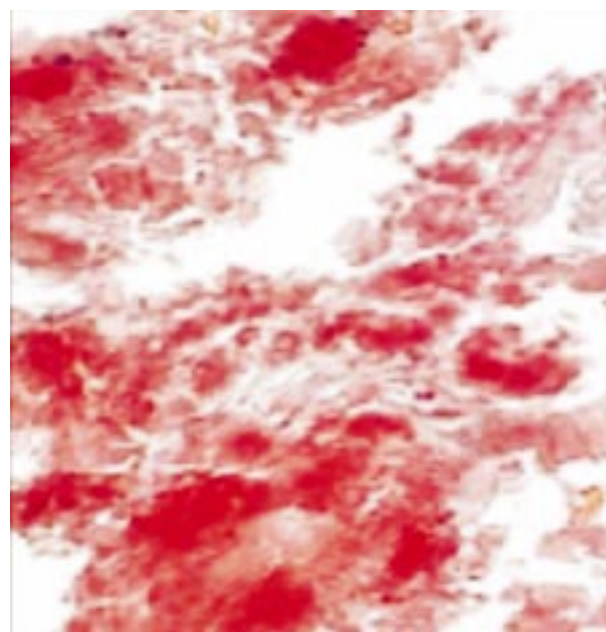
**SUMMARY** – Amyloidosis is a disorder characterized by localized or diffuse deposition of fibrillary proteins in the extracellular space, causing progressive damage to tissue structure and organ function. Any organ system of the body may be involved by amyloidosis. A case is presented of localized tracheal amyloidosis in a 62-year-old man treated for active lung tuberculosis. Among other procedures, diagnostic workup included bronchoscopy, which revealed tumor-like lesions of tracheal mucosa. Histologic analysis of the involved mucosa biopsy sample pointed to amyloidosis. Treatment with laser photocoagulation resulted in remarkable regression of the lesions.

**Key words:** *Amyloidosis – diagnosis; Respiratory tract diseases – diagnosis; Tracheal diseases – diagnosis; Amyloidosis – therapy; Bronchoscopy; Case report*

### Introduction

Amyloidosis is a disorder characterized by localized or diffuse deposition of fibrillary proteins in the extracellular space (mostly perivascularly)<sup>1-6</sup>. This leads to progressive damage to tissue structure and impaired function of the organs involved<sup>3</sup>. Amyloid is a protein of a unique ultrastructure, x-ray diffraction, and specific biochemical characteristics<sup>1-5,7,8</sup>. Amyloid deposits contain two components: a fibrillary component, making up to 80%-90% of the amyloid, and a non-fibrillary component consisting of P component and heparin sulfate protein. According to type of staining, amyloid (a) is seen as rose-red deposits on microscopy when stained with hematoxylin eosin (Fig. 1); (b) shows metachromasia upon staining with crystal violet; and (c) when stained with Congo red, it shows unique green diffraction when viewed through a polarizing microscope, which is also the most useful sole procedure to determine the presence of amyloid<sup>3,5,6</sup> (Fig. 2).

The etiology and pathogenesis of amyloidosis have not yet been fully clarified. However, some pathogenetic facts have been defined<sup>1,3,6</sup>. In primary amyloidosis (AL



*Fig. 1. On hematoxylin eosin staining, amyloid appears as rose-red deposits (light microscope).*

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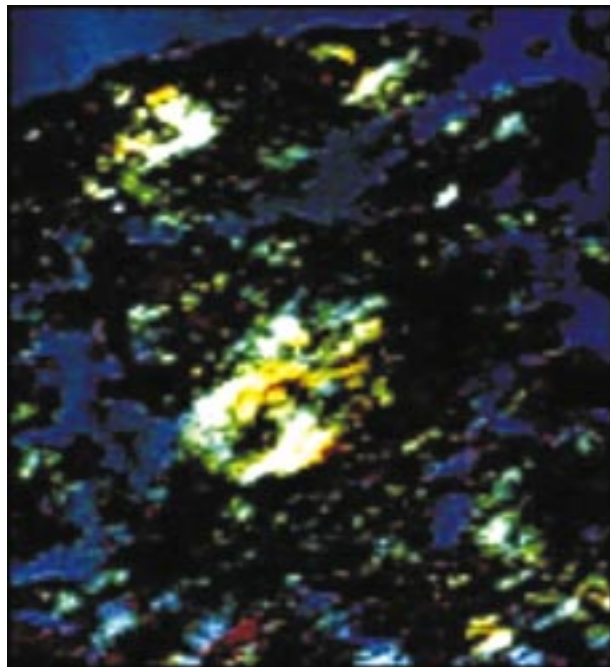


Fig. 2. On Congo red staining, amyloid appears as green deposit diffraction (polarizing microscope).

amyloidosis characterized by the presence of AL type of amyloid protein), there is a monoclonal population of the bone marrow plasma cells, which forms small lambda or kappa fragments or immunoglobulin clones (light chains). Secondary amyloidosis (AA amyloidosis) has been demonstrated to be a multifactorial process; during inflammation, the inflammatory mediator interleukin 1 stimulates hepatocytes for the production of serum amyloid (SAA), whereas monocytes and in part macrophages degrade SAA to insoluble protein A amyloid (AA)<sup>1-3,5,6</sup>. Amyloid formation may also be associated with the substance known as amyloid enhancing factor (AEF), most likely a cytokine, that contributes to the precipitated formation of secondary and probably other amyloid forms.

Clinical classification distinguishes three types of amyloidosis (based on the amyloid protein type)<sup>1,5</sup>:

- 1) AL types – (a) primary amyloidosis (no evidence of previous or concurrent disease)
  - (b) amyloidosis associated with multiple myeloma
- 2) AA types – (a) secondary (reactive) amyloidosis associated with chronic infectious diseases (osteomyelitis, tuberculosis) or chronic inflammatory diseases (rheumatoid arthritis)

(b) hereditary – familial amyloidosis (various renal and cardiovascular diseases)

- 3) other types – (a) localized amyloidosis (frequently manifesting as focal tumor-like lesions in isolated organs)
  - (b) amyloidosis associated with aging
  - (c) amyloidosis associated with longterm hemodialysis (presence of AB2M amyloid protein).

The symptoms of amyloidosis are nonspecific and depend on the underlying disease or organ system involved. For example, hepatic amyloidosis causes hepatomegaly (less frequently jaundice), whereas cardiac amyloidosis causes cardiomegaly and refractory decompensation, etc. Localized pulmonary forms of the disease and tracheobronchial amyloidosis, described as rare entities, are usually associated with dyspnea, cough and hemoptysis. Airway obstruction may induce distal atelectasis or recurrent pneumonia<sup>7,8</sup>. Diffuse infiltrating or nodular forms of amyloidosis are radiologically distinguished (90% and 10%, respectively)<sup>3</sup>. Nodules can be solitary or multiple<sup>9,10</sup>. Considering the progressive course of the disease, the mean survival prognosis is 12 months for AL amyloidosis (involvement of the lungs, heart and kidneys), and several years for localized forms of the disease (not associated with systemic amyloidosis)<sup>11</sup>.

The diagnosis of amyloidosis is made by identification of amyloid and consequential lesions of the organ involved. The following diagnostic methods are indicated in case of suspicion of amyloidosis: (a) biopsy of rectal mucosa and aspiration of abdominal subcutaneous adipose tissue + sample staining by use of staining techniques listed above; (b) or biopsy from some other site, e.g., skin, gingiva or the organ suspect to be involved (in case of suspect pulmonary amyloidosis, transbronchial biopsy of pulmonary tissue and biopsy of bronchial mucosa) + sample staining by use of staining techniques listed above; (c) electrophoretic and immunoelectrophoretic studies of serum and urine; and (d) possible DNA genome identification.

Therapy for amyloidosis is symptomatic, depending on the type of amyloidosis, the organ involved, and comorbidity. There is no specific therapy for any type of amyloidosis. Therapy is aimed at: (a) reduction of chronic antigenic, amyloid producing stimuli; (b) inhibition of the amyloid fiber synthesis and extracellular deposition; and (c) stimulation of the existing amyloid deposit degradation or mobilization.

In primary systemic amyloidosis, the use of particular therapeutic protocols (e.g., melphalan)<sup>12,13</sup> is indicated, attempting to act upon a part of the immunoglobulin light chain in the amyloid. Recent studies suggest the prednisolone/melphalan/colchicine regimen to prolong patient survival<sup>12</sup>. Colchicine is also used in the treatment of some hereditary-familial forms of the disease; it has been postulated to be able to block amyloid deposition). Organ transplantation is used in some severe cases of the disease (e.g., severe renal amyloidosis). Treatment with laser photocoagulation has proved successful for localized tracheobronchial amyloidosis.

#### Case Report

M.V., a 62-year-old man, was admitted to the hospital on April 24, 2003, with mild respiratory symptoms (hacking cough and minor breathing difficulties), auscultatory discrete crepitations on inspiration, basally on the left, and radiologic finding substantially suspect of a specific pulmonary process relapse (Fig. 3). In 1998, the patient was first treated at our institution for bacteriologically positive (smear and culture) pulmonary tuberculosis microscopically positive pulmonary tuberculosis. Also, the patient had been for years treated for a chronic mental disorder.

On admission, other physical findings and laboratory tests were normal, with the exception of elevated erythrocyte sedimentation rate (ESR; 32 mm/h). Spu-

tum samples were microscopically negative for bacil *Mycobacterium tuberculosis*, however, the first three cultures were BK positive.

The patient was treated with quadruple antituberculous therapy (streptomycin, ethambutol, rifampicin and pyrazinamide) in usual dosage until negative *Mycobacterium tuberculosis* (smear and culture) finding, then by triple antituberculous therapy (ethambutol, rifampicin and pyrazinamide). After six months of this therapy, slow regression of the specific changes indicated bronchoscopy to obtain material for bacil *Mycobacterium tuberculosis* analysis. It was then that lesions of the tracheal mucosa were first observed. The lesions resembled tumorous changes (narrowing tracheal lumen by about one third), with markedly hyperemic, edematous and submucosally infiltrated mucosa (Fig. 4). The lesions of 2 cm in length involved proximal trachea, located on its anterior wall. Aspirate, brush swab and biopsy sample were obtained from the site. Testing for *Mycobacterium tuberculosis* (aspirate and brush swab) produced negative results. Cytology revealed basal cell hyperplasia. Histology of the biopsy specimen showed a subepithelial homogeneous uniform growth, in which amyloid was demonstrated by staining with Congo red and polarized light imaging (Figs. 5 and 6).



Fig. 3. Radiologic finding on admission (April 24, 2003): infiltrating destructive specific lesions seen in the upper left lung.

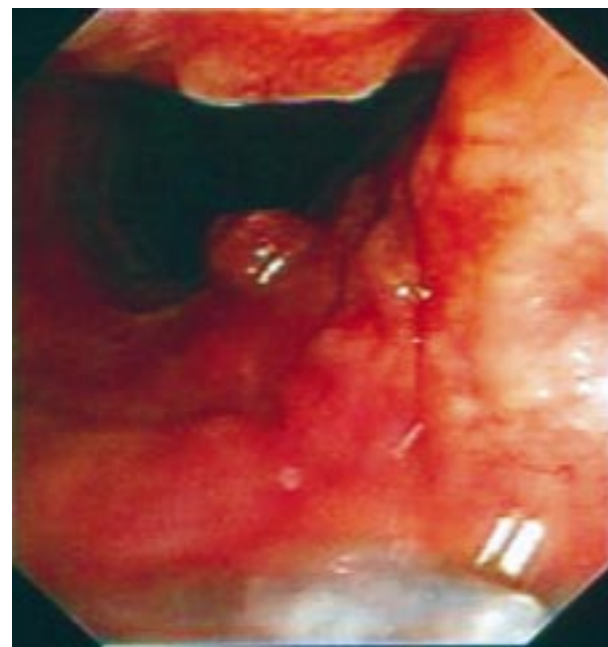
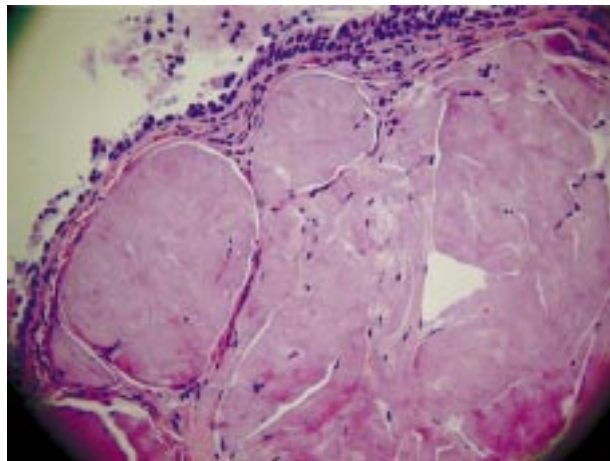
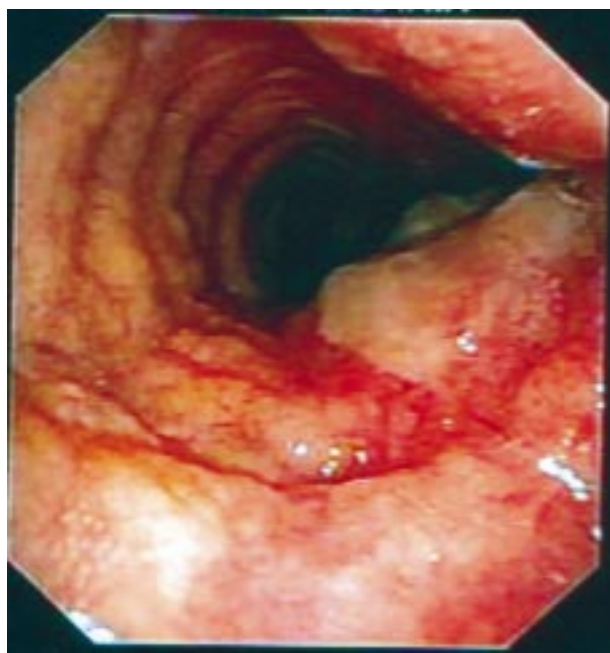


Fig. 4. Bronchoscopic finding of the trachea (October 2003): tumor-like lesions with hyperemic, edematous and submucosally infiltrated mucosa.

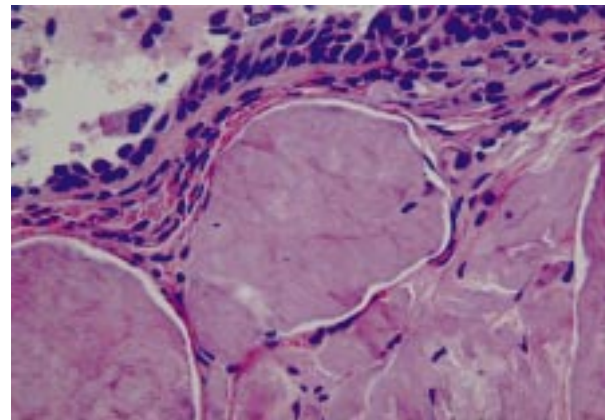


*Fig. 5. Histologic appearance of amyloid growths upon Congo red staining.*

Additional testing, performed for differentiation from other forms of amyloidosis and possible comorbidities produced normal results (serum protein electrophoresis; immunoelectrophoresis; complement C3 and C4; circulating immunocomplexes (CIC); cryoglobulins; autoantibodies including antinuclear factor (ANF), antiextractable nuclear antigen (ENA) and antineutrophil cytoplasmic autoantibody (ANCA); serum titer of rheu-



*Fig. 7. Tracheal bronchoscopy (April 2004): progression of lesions causing further narrowing of the tracheal lumen.*



*Fig. 6. A detail of histologic finding (magnification).*

matoid factors; 24-h urine protein; and upper abdominal ultrasonography). The patient was scheduled for re-hospitalization in April 2004 for clinical and therapeutic monitoring.

Control bronchoscopy at 6 months of the diagnosis showed overt progression with the lumen of proximal trachea narrowed by amyloid deposits (Fig. 7). However, the progression of pathologic alterations had not yet exerted any major effects on the overall clinical picture and alveolar gas in arterial blood.

Due to the progression of amyloid lesions, laser therapy in two therapeutic protocols was performed at a 2-month interval. Amyloid deposits were removed to a great extent by photocoagulation using fiberoptic bronchoscope and diode laser (focused power of 23 W) in local anesthesia (Figs. 8 and 9). On the patient's discharge from the hospital, 3-month control examinations were recommended. Bronchoscopy performed at 3 months of laser photocoagulation showed no disease progression (Fig. 10). Bronchoscopy findings obtained on the last 3-month control examination in April 2005, one year after laser therapy, the patient's condition was stabilized, free from progression of amyloid lesions (Fig. 11).

## Discussion

Localized pulmonary amyloidosis is defined as localized deposition of amyloid in respiratory tract and does not include amyloidosis associated with systemic amyloid deposition. The term refers to cases with involvement of the tracheobronchial tree or pulmonary parenchyma with localized (focal) or diffuse distribution. This form of the disease is very rare. Only five cases of amy-



*Fig. 8. Laser therapy: initial removal of amyloid deposits.*

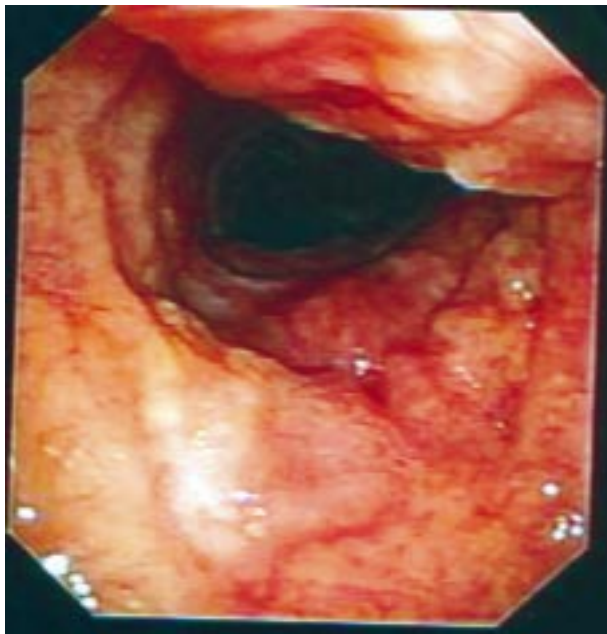


*Fig. 9. Laser therapy: the majority of amyloid deposits have been removed.*

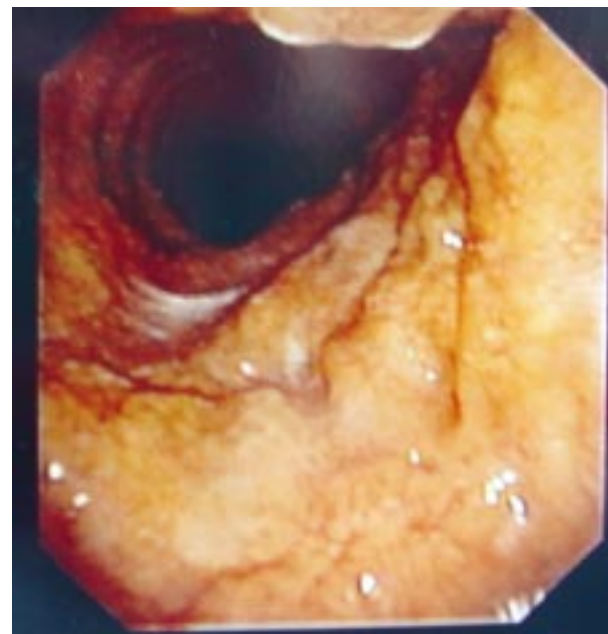
loidosis were reported in the literature during a 15-year period. Fifty-five cases of amyloidosis, 11 localized and only 4 of tracheobronchial localization, were diagnosed at Mayo Clinic from 1980 till 1993<sup>13</sup>. To our knowledge,

no case of localized pulmonary amyloidosis has been recorded in Croatia to date.

Patients with localized tracheobronchial amyloidosis may show variable bronchoscopy findings, from rela-



*Fig. 10. Tracheal bronchoscopy (3 months of laser therapy): no amyloid lesion progression.*



*Fig. 11. Tracheal bronchoscopy (April 2005): stabilized condition, no amyloid lesion progression.*

tively smooth amyloid plaques through tracheobronchial nodules or lesions of tumor-like appearance<sup>3</sup>. On differential diagnosis, tracheopathia osteoplastica, also a disease of unknown cause, with characteristic calcified or cartilaginous submucous nodules, should be taken in consideration. Although localized tracheobronchial amyloidosis is not associated with systemic amyloidosis, the course of the disease need not be always benign. In some cases, patients die from respiratory disturbances and recurrent pneumonia. Therapy of choice is laser photocoagulation<sup>3</sup>.

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### Sažetak

#### LOKALIZIRANA AMILOIDOZA DUŠNIKA

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Amiloidoza je poremećaj lokaliziranog ili difuznog nakupljanja fibrilarnih proteina u izvanstaničnom prostoru, koji progresivno oštećuju strukturu tkiva i funkciju organa. Poremećaj može zahvatiti bilo koji organski sustav u tijelu. Prikazuje se slučaj lokalizirane amiloidoze dušnika u 62-godišnjeg bolesnika liječenog zbog aktivne tuberkuloze pluća. Između ostalih dijagnostičkih postupaka učinjena je i bronhoskopija, pri čemu su uočene tumoru slične promjene na sluznici dušnika. Histološka pretraga uzorka dobivenog biopsijom sluznice sa zahvaćenog mjesta ukazala je na amiloidozu. Liječenje laserskom fotokoagulacijom rezultiralo je znatnim povlačenjem nastalih promjena.

**Ključne riječi:** *Amiloidoza – dijagnostika; Bolesti dišnoga trakta – dijagnostika; Bolesti dušnika – dijagnostika; Amiloidoza – terapija; Bronhoskopija; Prikaz slučaja*