

Pulmonary hypertension leading to right heart failure in a patient with iga gammopathy

YASHVIR SINGH SANGWAN (✉) •

BHAGWAN DASS

Internal Medicine, St Elizabeth's Hospital,

Belmont Avenue, Youngstown,

OH, USA 44501.

Pager: 330-613-9130

Phone/Fax: 330-318-8111

e-mail: yashvirsangwan@yahoo.co.in

YASHVIR S. SANGWAN • BHAGWAN DASS

ABSTRACT

Amyloidosis is a rare disorder characterized by the deposition of amorphous, extracellular, insoluble fibrillar protein in various tissues of the body. Pulmonary hypertension usually occurs in the last stages of the disease with co-existing left ventricular failure. Amyloidosis causing pulmonary hypertension in a patient with no evidence of left ventricular failure is rarely mentioned in literature. Here, we present a patient with IgA gammopathy presenting with pulmonary hypertension leading to progressive right heart failure and death.

Key words: amyloidosis, pulmonary hypertension, IgA gammopathy

The case

Our patient is a 73-year-old African-American lady who has had several hospital admissions over the past 2 years with the diagnosis of Congestive Heart Failure (CHF). The patient was on home oxygen therapy for CHF and coumadin therapy for atrial fibrillation. In September 2005 the patient suddenly worsened with severe and progressive shortness of breath (SOB) and increasing leg edema. Her weight increased from 72.5 kg to 113 kg and she became immobile. A 2-D echocardiogram revealed an ejection fraction (EF) of 55%, paradoxical septal motion with right ventricular overload, severe right atrial and ventricular dilatation, severe tricuspid regurgitation, mild-to-moderate pulmonary insufficiency, right ventricular (RV) end-diastolic pressure of 75 mmHg and severe pulmonary hypertension of 80 mmHg. She was stabilized with diuretics

and sent home. On recurrence of her symptoms she presented to our hospital in November 2005.

The patient had extreme dyspnea with swelling of the legs, thighs and abdomen. Her vital signs were stable. Physical exam of the cardiac and respiratory systems showed a significantly elevated jugular venous distention of 14 cm, bilateral bibasilar crackles, reduced air entry, an irregular heart-beat with a normal S1 and a fixed split S2, a 2/6 to 3/6 holo-systolic murmur (radiating through the whole precordium and changing with respiration), a laterally displaced point of maximal impulse and a right ventricle heave. The abdomen showed significant pulsatile hepatomegaly. The extremities had 4+ edema with chronic skin changes. Shotty adenopathy was seen in the cervical area and in the left supraclavicular area. Computed Axial Tomography (CAT) scan of the abdomen and pelvis showed abdominal ascites, small bilateral pleural effusions with pleural scarring, focal

aneurysms and dilatation of the splenic artery measuring up to 3 cm in size and dense calcification and granulomatous changes of the spleen. Electrocardiogram (ECG) showed normal sinus rhythm, incomplete right bundle branch block, T wave inversion in V1, V2, and V3 and RV hypertrophy.

We attempted to find the etiology of pulmonary hypertension and isolated right heart failure in this patient. There was no CAT scan evidence for chronic thrombo-embolic pulmonary disease or chronic obstructive pulmonary disease. A trans-esophageal echocardiogram (TEE) confirmed the echocardiogram findings and also revealed a possibility of patent foramen ovale. An extensive workup for Connective Tissue Disease explaining the pulmonary hypertension was non-diagnostic. A Sleep study showed only mild sleep apnea. The calcifications in the spleen could not be explained, as there was no old evidence of either sarcoid or histoplasmosis or old tuberculosis on

the imaging studies. Chronic fibrosing mediastinitis could be the only cause of the calcifications that could explain the significant right-sided heart failure. Other differential diagnoses entertained were vasculitis, amyloidosis and multiple myeloma.

Serum and urine protein electrophoresis with immunofixation revealed IgA gammopathy with normal IgM and IgG. The tests showed IgA lambda M-protein spike of 1900 mg/dl, IgG 1252 mg/dl (normal range 620-1400 mg/dl), IgM 179 mg/dl (normal range 45-250 mg/dl) and IgA 963 mg/dl (normal range 80-350 mg/dl). Gamma globulin was 1.9 gm/dl (normal range 0.7-1.6 gm/dl).

With the possibility of amyloidosis as a cause for the patient's symptoms, it was decided to biopsy the supraclavicular adenopathy but the patient refused this procedure. Bone marrow biopsy was not done due to the patient's poor status. The patient continued to have increasing respiratory distress and hypoxia despite medical treatment. She was made a Do-Not-Resuscitate (DNR) patient and expired in a nursing home in a few days.

Amyloidosis

Introduction

Amyloidosis is a disorder characterized by the deposition of amorphous, extracellular insoluble fibrillar protein in various tissues of our body causing widespread organ dysfunction and death (1). There are different types of subunit proteins – mainly AL and AA. AL is derived from the light chain of a monoclonal immunoglobulin and is seen in both primary and myeloma amyloidosis. AA is seen in secondary amyloidosis associated with chronic inflammatory diseases such as renal disease, syphilis, inflammatory bowel disease, rheumatoid arthritis, bronchiectasis, leprosy, osteomyelitis and certain cancers (2). End-stage renal disease and dialysis is associated with B-2 M amyloid and familial or senile amyloidosis show ATTR (transthyretin) amyloid. All amyloids bind Congo

red, produce apple green birefringence under polarized light and have a b-pleated structure.

Incidence

Immunoglobulin amyloidosis is rare with an incidence of 8 patients per million persons a year (3). 99% of patients are above the age of 40 years. (2)

Diagnosis

The initial screening is with immunoelectrophoresis and immunofixation of the serum and urine (4) revealing a monoclonal light chain in 90% of patients (5). In the rest, a subcutaneous fat aspirate, bone marrow biopsy or biopsies of the minor salivary glands will detect amyloid in 70-90% of patients (6). The bone marrow almost always will show a clonal population of plasma cells detectable by immunohistochemistry and immunofluorescence (7, 8). Direct biopsy of the affected organ will most likely be positive (9) although not usually needed (10). Radionuclide scans using radio labeled amyloid P component are capable of binding to amyloid deposits (11).

Clinical introduction

Fatigue, weight loss and periorbital purpura are the most common presenting symptoms (10). Consequently, a large proportion of these patients undergo detailed searches for an underlying occult malignancy (1). Macroglossia, the most specific physical finding, is positive only 9% of the time.

The four most common "syndromes" in immunoglobulin amyloidosis are: nephrotic range proteinuria (12), congestive heart failure (CHF) (5), unexplained hepatomegaly (13) and idiopathic peripheral neuropathy (14).

Kidney is the most frequently affected organ (35-50% patients) (15) usually presenting as unexplained nephrotic syndrome (16). Renal amyloidosis is seen in 10% of renal biopsies of non diabetics with nephrotic syndrome (12).

Cardiac involvement is seen in 25% patients, usually with unexplained CHF. Restrictive cardiomyopathy is seen in late stages (5). There is no systolic dys-

function till late in the disease. Echocardiogram frequently shows diastolic dysfunction, septal thickness of >12 mm (88% patients) (17,18), ventricular wall thickness >15 mm (19) and thickening of mitral and tricuspid valves. ECG usually shows low voltage (20) and QS complexes in leads V1 - V3 may be seen and interpreted falsely as a silent myocardial infarction (21).

16-25% of patients have hepatomegaly disproportionate to liver function tests abnormalities (22). Ascites is seen because of associated nephrotic syndrome and not due to portal hypertension as patients die of extrahepatic amyloidosis before portal hypertension can develop. Cholestatic jaundice is usually a preterminal finding. (23,24).

Salivary gland involvement can cause xerostomia (25,26). Gastric amyloidosis with nausea, vomiting and weight loss was seen in 8 and gastroparesis was seen in 3 of 769 patients in one series (27). Less than 5% of patients will show malabsorption. Amyloidosis can rarely present as pseudo-obstruction or ischemic colitis (28,29). Luminal narrowing and loss of haustrations are the most common radiological findings (30).

Peripheral neuropathy, usually in the lower extremities, is seen in 17% of patients. Muscle weakness (from neuropathy or vascular occlusion) and autonomic dysfunction are seen in approximately 65% of patients each. Muscle infiltration and pseudohypertrophy can be seen (31,32). Rarely temporal artery involvement may mimic giant cell arteritis. Calf, limb and jaw claudication might be seen (33-35). Fragile infiltrated blood vessels cause purpura and bleeds.

The respiratory system and gas exchange are usually preserved till late in the disease. Pulmonary amyloidosis may be localized or be a manifestation of systemic involvement. Local disease is classified as tracheobronchial, solitary nodular, multiple nodular and diffuse parenchymal (rare) (36). Patients may have dyspnea at rest or exertion and dry cough. Chest X-ray (CXR) may have features of interstitial lung dis-

ease. Amyloid deposits are seen on biopsy and may be predominant in the vascular walls or alveolar septa or both (37).

Hematological abnormalities like factor X deficiency, prolonged prothrombin time, platelet defects, decreased alpha 2 plasmin inhibitor, increased plasminogen may be seen (38,39).

Pulmonary hypertension

A Mayo Clinic study has reported 5 cases with the rare presentation of amyloidosis and pulmonary hypertension (PH) in patients with no secondary cause for PH and no evidence of left ventricle dysfunction. PH was found a median 73 days before death (2).

In patients with diffuse pulmonary amyloidosis, PH can be caused by either severe vessel wall infiltration with amyloid or by amyloid deposition in the alveolar septa, causing obliteration of

a significant proportion of the pulmonary capillary bed and pulmonary HTN developing concurrently with lung volume restriction (40).

Prognosis

Cardiac disease is the most relevant prognostic factor (41-43). 50% of patients will die of cardiac causes – CHF, ventricular fibrillation or asystole (44). A bad prognosis is seen in patients with EF < 50%, Creatinine > 1.3, neuropathy and diastolic dysfunction.

Therapy

Despite therapy, the median survival is only 17 months after diagnosis. In comparison, good-responders to treatment survive a median 90 months (6). Cycles of mephalan and prednisone are the treatment of choice (45). Response is measured by a 50% reduction in either urinary protein excretion or M-component or light chain or amyloid

precursor protein or serum alkaline phosphatase or a 2 mm reduction in cardiac wall thickness. Approximately 6.5% of patients exposed to melphalan develop a myelodysplastic syndrome. Median survival from onset is 8 months. Heart transplantation is effective for amyloidosis (46,47) with reported survival of 69-118 months. Myeloablative therapy with stem cell reconstitution (48) could work but has a treatment related mortality of 30-40% (49).

Conclusion

Amyloidosis should be considered in patients older than 40 years who have unexplained nephrotic syndrome, heart failure, idiopathic peripheral neuropathy or hepatomegaly. Diffuse pulmonary amyloidosis should be considered in the differential of unexplained pulmonary hypertension, especially in patients with systemic amyloidosis or multiple myeloma.

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