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Amyloidosis presenting with edema and heavy proteinuria: A case report

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Amyloidosis is the disease caused by extra-cellular accumulation of amyloid substance within various organs leading to progressive dysfunction of the organs. The organs that are more commonly involved include the kidney and the heart. This report is aimed topresent a case of systemic amyloidosis in a 69-year-old Thai woman who presented with edema and heavy proteinuria. She was referred to our hospital because of anasarca, suspected of amyloidosis. Her underlying diseases included diabetes mellitus, hypertension, hypothyroidism and chronic kidney disease stage 4 which were regularly and well controlled with medications.The physical examination confirmed the anasarca. Her vital signs were unremarkable. The blood tests revealed Hb10.2 g%, creatinine 1.98 mg%, FBS 96 mg%, HbA1c 5.6 %, albumin 2.4 g%, globulin 3.1 g%, cholesterol 149 mg%, positive ANA, FT4 1.18 mcg/dl, FT3 1.34 ng/ml, TSH 3.916 mIU/ml. The urinalysis showed no redblood cell, no white blood cell, no sugar, protein 4+ and the calculated urine protein to creatinine ratio (UPCR) was 8.8. The chest film revealed diffuse cardiomegaly and bilateral pleural effusion. The echocardiography showed granular sparkling at the interventricular septum which was highly specific for amyloidosis of the heart and moderate pericardial effusion. The abdominal fat pad biopsy was performed and found positive for Congo red with apparent apple green birefringence under polarized microscope.

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She was definitely diagnosed as nephrotic syndrome because of the systemic amyloidosis involving the heart and the kidney, not due to the diabetes, hypertension or systemic lupus erythematosus. Generally amyloidosis involving the kidney mostly accumulatesthe amyloid substance within the glomerulus and less commonly in the interstitium therefore the main manifestation is proteinuria which may vary from minimally asymptomatic to heavy proteinuria, 20 - 30 gram a day, accompanied by edema. If the patients are left untreated, the disease will progress to progressive kidney impairment and mortality.

Keywords: *Amyloidosis, heavy proteinuria, pleural and pericardial effusion.*

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โรคอะไมลอยด์โดสิส (amyloidosis) เป็นโรคที่มีการสะสมสารอะไมลอยด์นอกเซลล์ในอวัยวะต่าง ๆ หลายอวัยวะ มักจะทำให้อวัยวะนั้นค่อยเสื่อมหน้าที่ไป อวัยวะที่พบว่าถูกรบกวนบ่อย ได้แก่ ไต และหัวใจ ในการศึกษานี้เป็นรายงานผู้ป่วยที่เป็นโรคอะไมลอยด์ทั่วตัว ที่มาพบแพทย์ด้วยอาการบวม และโปรตีนรั่วทางปัสสาวะอย่างหนัก ผู้ป่วยหญิงไทยอายุ 69 ปีถูกส่งตัวมาพบแพทย์ด้วยอาการบวมทั้งตัวร่วมกับสงสัยว่าอาจมีโรคอะไมลอยด์ ซึ่งเดิมมีโรคประจำตัว ได้แก่ เบาหวาน ความดันโลหิตสูง ภาวะฮอร์โมนไทรอยด์ต่ำ และไตเสื่อมเรื้อรังระยะที่ 4 ได้รับการรักษาจากแพทย์อย่างต่อเนื่อง และคุมอาการได้ดี ตรวจร่างกายยืนยันว่าผู้ป่วยบวมทั้งตัวจริง สัญญาณชีพปกติ ตรวจเลือดพบฮีโมโกลบิน 10.2 กรัม%, creatinine 1.98 มก%, FBS 96 มก%, HbA1c 5.6 %, albumin 2.4 กรัม%, globulin 3.1 กรัม%, cholesterol 149 มก%, ANA ให้ผลบวก, FT4 1.18 ไมโครกรัม/ดล, FT3 1.34 นาโนกรัม/มล, TSH 3.916 mIU/มล ตรวจปัสสาวะไม่พบเม็ดเลือดแดง เม็ดเลือดขาวและน้ำตาล แต่โปรตีน 4+ คำนวณ urine protein to creatinine ratio (UPCR) ได้ 8.8 เอกซเรย์ทรวงอกพบว่าหัวใจโตทั่วไป และมี น้ำขังในช่องเยื่อหุ้มปอดทั้งสองข้าง ตรวจหัวใจด้วยเครื่องสะท้อนคลื่นเสียงความถี่สูง พบลักษณะที่เรียกว่า granular sparkling ที่ผนังกั้นหัวใจห้องล่าง ซึ่งมีความจำเพาะต่อโรคอะไมลอยด์ในหัวใจร่วมกับพบน้ำในช่องเยื่อหุ้มหัวใจพอประมาณ และเมื่อตัดชิ้นเนื้อเยื่อไขมันชั้นใต้ผิวหนังที่ผนังหน้าท้องออกตรวจ พบว่าให้ผลบวกต่อสี Congo red เห็นเป็น apple green birefringence เมื่อส่องด้วยกล้องจุลทรรศน์โพลาไรซ์ซึ่งมีความจำเพาะสูง ได้รับการวินิจฉัยว่าเป็นกลุ่มอาการ nephritic โดยเป็นมาจากโรคอะไมลอยด์ทั่วตัว ซึ่งมีทั้งที่หัวใจและไตไม่ได้เกิดจากโรคเบาหวาน ความดันโลหิตสูง หรือ systemic lupus erythematosus โดยทั่วไปโรคอะไมลอยด์ที่เข้าไตมักจะสะสมสารอะไมลอยด์ที่ glomerulus เป็นหลัก ส่วนที่รองลงมา คือ สะสมที่ interstitium ผู้ป่วยจึงแสดงอาการโปรตีนรั่วออกมาทางปัสสาวะเป็นหลัก ปริมาณ ที่รั่วมีทั้งที่ออกมาน้อยจนไม่ปรากฏอาการหรือออกมากถึงวันละ 20 - 30 กรัม จนทำให้เกิดภาวะบวมน้ำก็ได้ และถ้าผู้ป่วยไม่ได้รับการรักษาก็อาจทำให้ไตเสื่อมได้ และอาจเป็นสาเหตุของการเสียชีวิตได้

คำสำคัญ: *โรคอะไมลอยโดซิส, โปรตีนรั่วหนักในปัสสาวะ, น้ำขังในช่องเยื่อหุ้มปอดและช่องเยื่อหุ้มหัวใจ.*

Amyloidosis is the disease caused by extracellular accumulation of amyloid substance, i.e., low molecular weight fibrillar protein, deposited in certain organs leading to progressive impaired function of the organs. When it involves many organs simultaneously, it is called systemic amyloidosis.[1] The diagnosis of amyloidosis solely depends on positive Congo red stain of the pathology that is seen as the apple green birefringence under polarized microscope.

Amyloid substance can derive from various precursors. When amyloidosis involves the kidney, it is mostly commonly due to the amyloid light-chainamyloidosis or amyloid A amyloidosis whereas it may be transthyretin-related amyloidosis (ATTR), leukocyte chemotactic factor 2 amyloidosis (LECT-2), fibrinogen alpha and apolipoproteins A1, A2, and A4 in the minority.[2] The clinical manifestations depend on the precursors and the amount of the amyloid substance as well as the specific sites of the involvement within the kidney. Proteinuria may be asymptomatic if the amyloidis is accumulated in the tubules or vasculatures[3] or heavy proteinuria leading to edema or even nephrotic syndrome that impairs kidney functions when it involves the glomerulus. Therefore, when the patients have heavy proteinuria, glomerular range (proteinuria >3.5 gram a day), impaired glomerular filtration or nephritic syndrome are encountered; each problem is an indication for the kidney biopsy to verify the specific cause and, hence the appropriate treatments. And if the amyloid substance in the kidney is demonstrated the AL type[4,5], further investigations such as the serum or urine protein electrophoresis, immunofixation and free light chain[6] must be performed to see whether there is the monoclonal gammopathy from plasma cell neoplasm.

The aim of this study is to report a case of anasarca and heavy proteinuria due to systemic amyloidosis.

Case Report

A 69-year-old Thai woman was admitted at Fort Suranaree General Hospital because of anasarca for a week, she had no paroxysmal nocturnal dyspnea and no fever. She neither had history of smoking or drinking. Her underlying diseases included diabetes, hypertension, hypothyroidism and chronic kidney disease stage 4; they were all well and regularly controlled with the medications. The physical examinations confirmed the anasarca with normal vital signs. Her chest film showed cardiomegaly and bilateral pleural effusion. Her urine protein was 4+ and the calculated urine protein to creatinine ratio (UPCR) was 8.8. Her blood tests included: serum albumin 2.6 g%, ANA positive 1:2,560; no HBsAg; no anti-HCV. Her thyroid function test was consistent with subclinical hypothyroidism. Her echocardiography revealed left ventricular ejection fraction (LVEF) of 66%, and the granular sparkling pattern at the interventricular septum with moderate pericardial effusion. She was referred to our hospital under suspected amyloidosis that produced heavy proteinuria.

Additional investigations in our hospital included: Hb 10.2 g%, Hct 31.1%, white blood cell (WBC) 5,900/mm^3, neutrophil (N) 75%, lymphocyte (L) 12%, absolute lymphocyte 708/mm^3, platelets 248,000/mm^3, MCV 86.6 fl, MCH 28.3 pg, FBS 96 mg%, HbA1c 5.6%, BUN 41.9 mg%, creatinine

1.98 mg%, eGFR23 ml/m^2/min, Ca 8.9 mg%, P 3.15 mg%, albumin 2.4 g%, globulin 3.1 g%, cholesterol 149 mg%, direct bilirubin 0.1 mg%, total bilirubin 0.4 mg%, AST 27 U/L, ALT 9 U/L, alkaline phosphatase 48 U/L, Na 139 mEq/L, K 4.29 mEq/L, Cl 105 mEq/L, CO_2 23.2 mEq/L, negative HBsAg, anti-HCV and HIV antigen/antibody.

Urinalysis: pH 6.0, protein 4+, no sugar, no blood cell.

FT4 1.18 (normal 0.6 - 1.6 mcg/dl), FT3 1.34 (normal 2.39 - 6.79 ng/ml), TSH 3.916 (normal 0.38 - 5.33 mIU/ml), consistent with the sick euthyroid syndrome

Immunofixation electrophoresis: Kappa 122.0 mg/l, Lambda 55.9 mg/l, Kappa /Lambda 2.1; no paraproteinemia detected

The chest film persistently showed diffuse cardiomegaly and bilateral pleural effusion.

The echocardiography showed the LVEF = 72% and moderate pericardial effusion.

The bone marrow pathology revealed cell: fat ratio = 30:70, myeloid: erythroid ratio = 2:1, erythroid, myeloid, megakaryocyte morphology: appropriate and unremarkable, lymphoid cell andplasma cell: not increased, no fibrosis, no granuloma. Diagnosis: normocellular trilineage marrow, no evidence of malignancy.

The ultrasonography of the upper abdomen showed increased echo of the renal parenchyma of bilateral kidneys, no demonstrated obstruction and no renal stone. Right kidney 10.7 x 5 cm, left kidney 10.5 x 4.9 cm. Normal urinary bladder and ascites were detected.

The abdominal fat pad biopsy: the Congo red staining showed positive apple green birefringence under polarized light microscope. Diagnosis: Amyloidosis.

She was finally diagnosed as having nephrotic syndrome due to systemic amyloidosis involving the heart and the kidney and was treated with colchicine and azathioprine and other supportive managements.

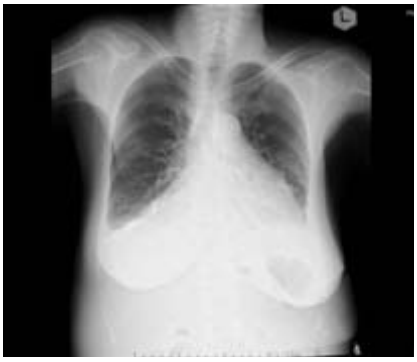

Figure 1. The chest film showed huge cardiomegaly and bilateral pleural effusion.

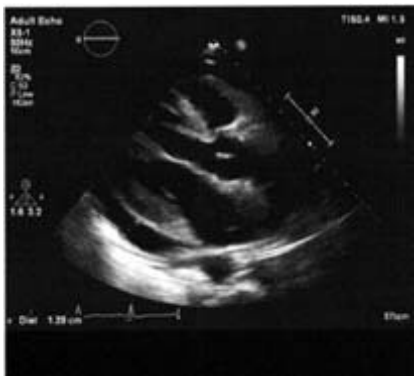

Figure 2. The echocardiography showed the characteristics of the myocardium of the amyloidosis patient.

Discussion

Our case presented with anasarca without paroxysmal nocturnal dyspnea, no liver disease whereas her urine test had protein 4+ and calculated UPCR of 8.8, consistent with the nephritic proteinuria (more than 3.5 gram a day); and her serum albumin

was less than 2.5 – 3 g%. All these suggested the nephrotic syndrome although her serum cholesterol was less than 350 mg%.[7]

Besides diabetes[8] or hypertension[9], systemic lupus erythematosus[10] can also be a cause of heavy proteinuria because its criteria fulfilled with the positive ANA, the effusion in the pericardial and pleural cavities possibly representing polyserositis, lymphopenia and proteinuria. Other possibility is an infiltrative disease such as amyloidosis[11] or lymphoma[12] because the kidney size did not decrease. So, the kidney pathology should have been studied for finding the specific cause of heavy proteinuria. But it was not performed because amyloidosis was documented on the abdominal fat pad biopsy and it was also presumed to account for the pathology of the kidney. Actually, amyloidosis was found in 14.2% of patients with nephrotic syndrome who were 50 years old or above.[11]

As the granular sparkling pattern at the interventricular septum on the echocardiogram was highly suggestive of amyloidosis of the heart[13], the abdominal fat pad, the easily accessed and recommended site for screening of amyloidosis was biopsied; it had the sensitivity of 73% and specificity of 90%. Although the kidney biopsy had nearly 100% sensitivity if stained with the Congo red under polarized microscope[14], it had more risk of bleeding due to the amyloid accumulation in the kidney tissue.[15]

The most common site of the amyloid accumulation within the kidney is the glomerulus, others in decreasing order are the tubulo-interstitium and the vasculature. So the manifestation is mainly proteinuria particularly albumin. The amount may vary from minimal to heavy, 20 - 30 g a day leading to hypoalbuminemia and anasarca[16] as seen in our case. Unless treated, the disease will slowly progress until finally renal failure and become one of the major causes of death.

Conclusion

A 69-year-old Thai woman presented with nephritic syndrome for a week, and kidney biopsy was performed. However, the abdominal fat pad was pathologically proved to be amyloidosis which also presumably and was accounted for the pathology in the kidney. Therefore, her nephrotic syndrome could be properly managed.

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