AA amyloidosis in a patient with a chronic inflammation of an esophageal anastomosis, the stomach and the mediastinum

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Amyloidosis is a disease known for many years, in which various abnormal proteins deposit extracellularly in multiple organs and tissues, hindering their function. One of the multiple types of this condition is AA amyloidosis, which occurs in less than 1% of patients with a chronic inflammatory state.

This case report describes a 67-year-old male with a history of tuberculosis and hemoptysis, type B hepatitis and esophageal reconstruction surgery which he underwent many years ago after a lye burn in 1969. He presented in 2013 with proteinuria of 2.7 g/24h, haematuria and splenomegaly with accompanying lymphocytosis. Suspecting a systemic connective tissue disease, a kidney biopsy was planned, to which the patient did not give consent. He returned to the clinic 14 months later, with proteinuria higher than 5 g/24h, signs of emaciation and albumin concentration of 1.7 g/dl. Between hospitalisations, a splenectomy was performed due to a splenic diffuse red pulp lymphoma. A kidney biopsy, performed after admission, revealed AA amyloid deposits. Various imaging techniques and autoimmune antibody panel tests were introduced in differential diagnosis to find the primary inflammation. A PET-CT scan located diffuse inflammation in the esophageal anastomosis, the stomach and the mediastinum. In order to control proteinuria, Methyloprednisolone pulse treatment and Cyclosporin were introduced, with short-lasting benefits. The patient's renal failure gradually progressed, which prompted taking up hemodialysis. The patient was hospitalised later multiple times due to significant proteinuria.

We present a diagnostically challenging case report, in which AA amyloidosis was probably caused by an inflammation of an esophageal anastomosis, the stomach and the mediastinum lasting over 45 years.

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Amyloidoza AA u pacjenta z przewlekłym zapaleniem zespolenia przełyku, żołądka i śródpiersia

Amyloidoza jest chorobą znaną od wielu lat, w której liczne nieprawidłowej budowy białka odkładają się zewnątrzkomórkowo w wielu narządach i tkankach, upośledzając ich funkcjonowanie. Jedną z wielu odmian tego schorzenia jest amyloidoza AA, która występuje u mniej niż 1% pacjentów, u których stwierdza się przewlekły stan zapalny.

Opisano przypadek 67-letniego mężczyzny z wywiadem gruźlicy i krwioplucia, zapalenia wątroby typu B i przebytej przed wieloma laty rekonstrukcji przełyku po oparzeniu ługiem w roku 1969, który zgłosił się w roku 2013 do kliniki z powodu białkomoczu 2,7 g/24h, krwiomoczu i splenomegalii z towarzyszącą limfocytozą. Podejrzewając układową chorobę tkanki łącznej zaplanowano biopsję nerki, na którą pacjent nie wyraził wówczas zgody. Pacjent wrócił do kliniki 14 miesięcy później, z białkomoczem wyższym niż 5 g/24h, objawami wyniszczenia i stężeniem albumin 1,7 g/dl. Pomiędzy hospitalizacjami została wykonana splenektomia z powodu rozlanego chłoniaka z małych komórek B miazgi czerwonej śledziony. Po przyjęciu wykonano biopsję nerki, która wykazała złogi amyloidu AA. Do diagnozy różnicowej pierwotnej przyczyny stanu zapalnego użyto technik obrazowych i testów wykrywających przeciwciała obecne w chorobach autoimmunologicznych. W badaniu PET-CT stwierdzono rozlane zmiany zapalne w odtworzonym przełyku, żołądku i śródpiersiu. Podjęto próbę ograniczenia białkomoczu stosując Metyloprednizolon w leczeniu pulsacyjnym oraz Cyklosporynę, uzyskując przejściową poprawę. Stwierdzono stopniowe narastanie niewydolności nerek, co spowodowało włączenie leczenia hemodializami. Pacjent był następnie kilkakrotnie hospitalizowany z powodu znacznego białkomoczu.

Przedstawiono przypadek chorego, trudny diagnostycznie, u którego przyczyną amyloidozy AA prawdopodobnie było zapalenie zespolenia przełyku, zapalenie żołądka oraz śródpiersia o ponad 45-letnim przebiegu..

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Background

Amyloidosis is a rare disease. It is the result of extracellular depositing of abnormally formed fibrillar proteins, collectively referred to as the amyloid. The malformaton causes the proteins to lose their solubility, which aids their settling [1].

Numerous types of amyloidosis can be distinguished regarding the proteins precursory to the amyloid. The most common one is AL, or primary, where immunoglobulin light chains are the main component of the amyloid. It is primarily associated with multiple myeloma. Among the multiple clinically important amyloidoses we can also mention hemodialysis-associated amyloidosis, where 2 microglobulin acts as the precursor, or familial, linked to defective transthyretin.

AA amyloidosis, also known as secondary, is a consequence of chronic inflammation [1]. As a result of the inflammation, acute phase proteins are produced. One of them, SAA (Serum Amyloid A), is synthetised in hepatocytes. When high blood concentration of SAA persists, a small portion of it, called the AA protein, separates and deposits in various tissues and organs, most commonly the kidneys, with proteinuria as the first symptom [2]. AA amyloidosis occurs in less than 1% of patients with a chronic inflammatory state [2]. The diagnosis needs to be confirmed with a biopsy, most commonly of the kidney. Duodenal, rectal or gingival tissues can also be used [1,3-5]. The Kongo red-stained amyloid under polarized light shows a so-called apple-green birefringence [1]. Prognosis in amyloidosis is unfavorable, mainly because of the lack of therapeutic options specific to the amyloid. Renal failure continues to be the main cause of death in these patients [2].

Case report

In 2013, a 67-year old male was admitted to the clinic with a history of tuberculosis, hemoptysis, deep venous thrombosis (DVT), stomach ulcerative disease, type B hepatitis, esophageal reconstruction surgery after a lye burn in 1969 and a family history of neoplasms. He presented with proteinuria of 2.7 g/24h, haematuria and splenomegaly with accompanying lymphocytosis. On admission, his clinical state was quite good, creatinine level was 0.9 mg/dl with serum albumin of 3.2 g/dl. The patient was suspected to suffer from a systemic connective tissue disease and qualified for a kidney biopsy, to which he did not give consent. The patient was discharged with advice of nephroprotective treatment. 14 months later, the patient returned, with proteinuria of 5.4 g/24h, creatinine of 1.1 mg/dl and serum albumin of 1.7 g/dl. Between hospitalisations the patient was treated due to a splenic diffuse red pulp lymphoma, and a splenectomy was performed. This time, a kidney biopsy was collected. It revealed A amyloid deposits in all of the glomeruli. Additionally, stromal lymphocyte infiltration and tubular atrophy were found. SAA blood concentration was 3.7 mg/dl (1.0-2.5 mg/dl), while 2 microglobulin was 3.3 g/dl (0-3g/dl). Free light chain ratio in plasma and urine was normal. Renal parameters were not impaired, with creatinine of 1.1 mg/dl. The patient was diagnosed with AA amyloidosis. Differential diagnosis was needed to find the underlying cause of this condition. The patient tested negative for ANCA and anti-GBM antibodies. ANA antibodies' titre was 1:320. The laboratory tests and clinical symptoms did not give a basis to diagnose SLE. An abdominal ultrasonogram did not bring any useful findings. A CT scan of the chest, abdomen and pelvic regions showed only paratracheal lymph nodes enlarged to 16 mm. The organs were described as free of focal lesions. To exclude tuberculosis, a chest X-ray was performed, which did not show any signs indicative of infection. Another X-ray, of hands and feet, disproved rheumatoid arthritis. Rheumatoid factor was determined to be lower than 10. A consulting hematologist did not link the splenic lymphoma with amyloidosis. A colonoscopy, which was performed to exclude inflammatory bowel diseases, showed no lesions. A gastroscopy showed an ulcer 2 centimeters below the esophageal anastomosis, covered with fibrin. A tissue specimen was collected and histopathologically proven to contain active inflammation. In the X-ray of the esophagus, residual contrast suggested a possibility of a small diverticulum in the area of the anastomosis. A full-body PET-CT scan using ^{18}F-FDG located diffuse inflammation in the esophageal anastomosis (SUV 3.8), the stomach and the mediastinum (SUV 3,3). Continous growth of creatinine levels was found to increase up to pre-dialysis values. The patient's SAA levels were higher, reaching 4.2 mg/dl, while renal function still gradually worsened, which prompted taking up hemodialysis. In order to manage the inflammation, an anti-inflammatory treatment regime was introduced, consisting of Methylprednisolone, continued with Prednisolone on an outpatient basis. Later, because of unsatisfying results and increasing proteinuria, Cyclosporin was added to the scheme. The patient suffered from deproteinisation, with serum albumins as low as 1.2 g/dl, and total protein of 2.8 g/dl. A PEG tube was inserted to improve the patient's poor nutritional state, skip the esophageal anastomosis and aid removal of the lingering content. Over the course of later treatment, while the patient's state temporarily improved, he required many hospitalisations and chronic dialysis treatment. He died in the course of sepsis, after ca. 2 years of dialysis.

Discussion

Despite the advancements made in understanding and managing this complex disease, amyloidosis continues to pose a diagnostic and therapeutic challenge to clinicists. The first symptom, as in our patient, is most often proteinuria, as AA amyloidosis tends to damage the kidneys. This proteinuria is not correlated with hyperlipidemia [3]. A kidney biopsy, most diagnostic in patients with proteinuria, is needed to determine whether or not the patient suffers from amyloidosis. If the patient is not suitable for a kidney biopsy, alternatives are an abdominal fat biopsy (used mainly in AL amyloidosis) or a duodenal biopsy, which can be used in AA amyloidosis and has a higher sensitivity than biopsies from other parts of the gastrointestinal tract [4,5]. Our patient's biopsy revealed findings indicative of AA amyloidosis: A amyloid deposits in all of the glomeruli, with stromal lymphocyte infiltration and tubular atrophy.

The treatment of AA amyloidosis remains a matter of controlling the underlying disease or inflammatory state in order to minimise further amyloid deposition. Finding the cause of AA amyloidosis is a multi-faceted problem, as authors from around the world inform about various states which may lead to, or favor developing AA amyloidosis. Emerging topics are type B hepatitis, intravenous drug use and obesity to name a few [6-9]. Taking that into consideration, the most important step in differential diagnosis is to evaluate the patient's state and history to determine if there are any significant anchor points from which to start. Autoimmune diseases, systemic connective tissue diseases, of which rheumatoid arthritis continues to be the most frequent, neoplasms or infections such as tuberculosis can all lead to AA amyloidosis. It is also worth mentioning that the most common neoplasms leading to AA amyloidosis are RCC and Hodgkin lymphoma [1]. In our patient, who had a history of tuberculosis, type B hepatitis and was diagnosed with and treated for splenic diffuse red pulp lymphoma, we assessed them as not connected with amyloidosis. The biggest challenge regarding amyloidosis is the differential diagnosis, therefore it is crucial to carefully assess the patient's possible unique and specific underlying causes, as was the case with this patient. In our patient, the esophageal anastomosis was ultimately found to be the inflammation's location. The inflammation might have lasted even longer than 45 years without giving notable symptoms. This is enough time for AA amyloidosis to develop, and in our patient it seems that the disease had been progressing for a significant time. It is worth remembering that chronic inflammation is required to induce AA amyloidosis. Therefore, it is most efficient to start the work-up with the most commonly observed causes, such as autoimmune diseases, including rheumatoid arthritis, and Crohn's disease [10]. Searching for neoplasms and infections is the next step to take, preferably simultaneously.

While the incidence rate of AA amyloidosis tends to lower [11,12], there still are not enough therapeutical options specific to the amyloid. The main strategy of controlling the disease continues to be the suppresion of the underlying cause to limit the production of SAA. In our patient, in order to reduce inflammation, a PEG tube was inserted in an attempt to administer

food avoiding the upper gastrointestinal tract. Besides standard anti-inflammatory drugs used in the treatment of various inflammatory conditions, it is possible to introduce high-dose colchicin, which in certain diseases, such as FMF, is able to induce remission [13]. Canakinumab (an anti IL-1 antibody) was found to be a treatment option in patients with AA amyloidosis secondary to FMF who are resistant to colchicine [14]. Renal transplantation is also a therapeutic option, albeit patients with amyloidosis are more prone to post-transplantation complications, such as heart failure and infections, therefore a careful patient selection is needed beforehand [15]. The clinical state of our patient did not allow us to consider renal transplantation therapy.

Regarding AA amyloid-specific treatment options, there is a significant lack of those which can be used in daily practice. Further development of amyloid-specific drugs is needed to provide widely accessible, universal therapeutic options in a wide array of clinical indications which would improve the patients' quality of life.

Follow-up in patients with AA amyloidosis is most commonly associated with SAA blood levels. Both renal prognosis and survival rate are correlated with SAA levels. SAA as high as twice the upper limit increases the risk of death five fold. Lower levels of SAA signify better survivability and may even indicate regression of amyloid deposition [16]. Our patient's SAA levels indicated a risk of severe course of the disease, which taking into consideration his follow-up declining renal function proved to be true. Acceptable main condition control is crucial in achieving long-term kidney function and patient survival. Renal replacement therapy with renal transplantation may be a consequence of AA amyloidosis [17].

In conclusion, our patient suffered from an inflammation possibly spanning over 45 years, which might have been the cause of a long-term high concentration of serum SAA and amyloid deposits in the kidneys. Finding such chronic inflammatory state is crucial in AA amyloidosis and enables causal treatment and satisfactory renal function control. Until amyloid-specific therapeutic options become viable for everyday use, attempting causal treatment of the underlying condition will continue to be the basis of therapy.

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