Successful pregnancy in the patient with AA amyloidosis complicating Crohn's disease

Systemic AA amyloidosis is a rare complication of chronic inflammatory diseases. The mean time of developing systemic amyloidosis is about 17 years of an uncontrolled inflammatory process. Therefore, amyloidosis AA is rarely observed in young females. The nephrotic syndrome caused by kidney involvement is one of the most common and serious manifestations of the disease. The case concerns a woman, aged 32, with a history of Crohn's disease complicated by AA amyloidosis and nephrotic syndrome who gave birth to a healthy son after effective treatment of the underlying disease

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Prawidłowa ciąża u chorej z amyloidozą AA w przebiegu choroby Crohna

Układowa amyloidoza AA jest rzadkim powikłaniem przewlekłych chorób zapalnych. Średni czas po którym dochodzi do rozwoju uogólnionej amyloidozy AA w przebiegu niekontrolowanego procesu zapalnego wynosi 17 lat. Z tego powodu amyloidoza układowa AA rzadko jest obserwowana u młodych kobiet. Zespól nerczycowy do którego dochodzi na skutek zajęcia nerek w przebiegu amyloiozy AA jest jednym z najpoważniejszych i najczęstszych objawów choroby. Przedstawiamy historię choroby 32 letniej kobiety, z zespołem nerczycowym i amyloidozą AA w przebiegu chorobą Crohna, która urodziła zdrowego chłopca po skutecznym leczeniu choroby podstawowej.

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Introduction

Systemic AA amyloidosis is a rare complication of chronic inflammatory diseases. The annual incidence of AA amyloidosis in Europe is about 1-2 cases per million [1]. In developed countries AA amyloidosis is mainly a complication of rheumatoid diseases (rheumatoid arthritis [RA], juvenile idiopathic arthritis, spondyloarthritis, psoriatic arthritis) or inflammatory bowel disease, especially Crohn's disease (CD) [1].

There are some differences in the frequency of systemic amyloidosis in the world. In developing countries, AA amyloidosis is more common, and is a complication of chronic infectious diseases, such as tuberculosis, bronchiectasis, furunculosis or schistosomatosis [2].

The nephrotic syndrome caused by kidney involvement is one of the most common and serious manifestations of the disease. Nephropathy occurs in 97% of patients with systemic AA amyloidosis [3].

The aim of AA amyloidosis treatment is to control the primary inflammatory process in order to maintain acute phase proteins within normal levels. When serum amyloid A (SAA) is below 10 mg/l, the amyloid deposits will gradually regress from tissues and symptoms of disease will disappear [4]. AA amyloidosis develops slowly. The mean time of developing systemic amyloidosis is about 17 years (4-40) of an uncontrolled inflammatory process [3]. Therefore, AA is rarely observed in young females. The exception is FMF, which starts in a childhood. Amyloidosis is observed in 90% of patients with FMF at the age of 20.

Fertility in AA amyloidosis is decreased by complications of disease, co-morbidities and treatment [5]. The case series of pregnant patients with AA amyloidosis comes from Europe and Asia and concerns patients with FMF [6]. In patients with FMF, effective control of disease is achieved thanks to colchicine therapy. Discontinuation can cause acute peritonitis and cause preterm delivery or abortion [7]. Several complications of pregnancy were observed in FMF patients with AA amyloidosis: preeclampsia, preterm delivery and child growth retardation [7]. To the best of our knowledge, no case of pregnancy in the patient with AA amyloidosis complicating CD had been described previously.

Case report

The case concerns a woman, an office worker, aged 32, with a history of CD complicated by AA amyloidosis, who gave birth to a healthy son in March 2014.

The patient's history revealed diarrhea and abdominal pain, which started when the patient was 16 years old. Despite numerous hospitalizations and additional examinations, a proper diagnosis was not made until 2008.

In February 2008, the patient, then aged 30, was admitted to the Department of Ne-

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phrology because of nephrotic syndrome. Physical examination upon admission revealed extensive edemas of subcutaneous tissue, expressed mostly on the lower leg, asthenic constitution (BMI 17), a tender abdomen without perceptible pathological resistance, RR was 90/60 mmHg.

The patient's laboratory results were as follows: hemoglobin 14.0 g/l, C- reactive protein (CRP) 7.5 mg/l, creatinine 0.62 mg/dl, total serum protein 51 g/l; albumin 28 g/l, total cholesterol 207 mg/l, daily protein loss was 14 gram (Tab. I).

During ultrasound examination both kidneys appeared normal, although a thickening of the small intestine wall was revealed. In a kidney biopsy, deposits were diagnosed in all renal glomeruli - staining with Congo red confirmed the presence of amyloid. Moreover, ulceration in the terminal section of the small intestine was detected endoscopically, and in the subsequent histological examination of the gastrointestinal tract changes typical for Crohn's disease were described.

Based on the clinical picture and additional examinations, a diagnosis of amyloidosis AA with nephrotic syndrome in the course of CD was established. Initially, before the biopsy, the patient was treated with methylprednisolon, whose dosage was then reduced, along with the addition of enteric budesonid after this diagnosis.

In April and May 2008, 3 doses of infliximab were administered, which resulted in quick remission of clinical symptoms such as abdominal pain, diarrhea and fever. However, elevated CRP and the laboratory symptoms of nephrotic syndrome were still present. In May 2009, after a year of treatment, a decrease in proteinuria and an increase in the albumin level was observed with a continued, slight increase in CRP (4.7-5.9 mg/l). Therefore, in October 2009 azathioprine was introduced, which led to the normalization of CRP in May 2010.

Since November 2011, the concentration of serum amyloid A was monitored - a normalization of the SAA level was observed in March 2011. In the meantime, the patient received two consultations at the National Amyloidosis Centre in London, where, based on SAP scintigraphy, the presence of amyloid deposits in the kidneys, adrenals and spleen was confirmed. During the next two years (2011 and 2012), the patient was in good general health, with no clinical symptoms of CD and a BMI of 18.5. In May 2012, azathioprine was discontinued: the proteinuria decreased gradually and reached 0.28 g/ 24 h in December 2012.

When complete remission of CD and nephrotic syndrome was achieved, the patient decided to become pregnant. Pregnancy started in autumn 2013. Treatment with budesonide and antihypertensive drugs continued. No symptoms from the GI tract were observed. The only complication during pregnancy was a mild infection of the lower urinary tract. In a laboratory test, a rise in daily proteinuria and decrease in serum albumin was observed (Tab. I). In February 2014, the daily proteinuria was 2.16 g/24h and serum albumin 23 g/l.

On 15 March 2014, the patient gave birth to a healthy son (2500 grams, 50 cm, an Apgar score of 10 points). In October 2014, both mother and son were in very good health. The patient is still breast -feeding, taking budesonide (3 mg a day), metoprolol (50 mg a day) and nitrendypine (2 x 15 mg). Her daily proteinuria was 0.27 g/24 h.

Discussion

Systemic AA amyloidosis is a devastating disease. In many patients it is the most severe complication of a long-lasting inflammatory process. In the case presented nephrological complications of AA amyloidosis helped to establish a diagnosis of CD and to start the proper treatment, which enabled the patient to become pregnant.

In patients with CD in remission, conception is unaffected [8]. Problems with fertility particularly concern females with a history of inflammatory processes in the fallopian tubes and who have undergone some surgical procedures. An active inflammatory process have a negative impact on pregnancy and the health of a child. In an uncontrolled disease, the risk of abortion, preterm delivery and low birth weight increases [9]. Pregnancy can alleviate the further course of the disease. The number of relapses was lower in females who were pregnant compared to those who were not [10]. The frequency of disease relapses is similar in pregnant CD patients compared to other females with CD [9]. It seems that many drugs are safe during pregnancy with a low risk of teratogenicity. The exception is methotrexate (MTX), which is strictly contraindicated in pregnancy. MTX is highly teratogenic and should be discontinued 3–6 months before conception [11].

Aminosalycylates, steroids, azathioprine and 6-mercaptopurine are safe in pregnancy according to ECCO [12]. Patients treated with sulfasalazine must substitute folic acid in a dose of 2 mg/day [10,12]. Mesalazine has no impact on folic acid synthesis, and folic acid substitution is not recommended [12]. Prednisone and prednisolone are preferred steroids in pregnancy, because they are inactivated by placental 11 beta-hydroxydehydrogenase [11]. Use of budesonide in pregnancy is probably safe [12]. On the basis of clinical observation, there is no evidence that any TNF inhibitor has a negative impact on pregnancy nor on the fetus [11,12]. These drugs are not recommended after 20-22 weeks of pregnancy because of possible transplacental transport [13].

In relapses of CD during pregnancy, systemic steroids are preferred. In the first trimester, anti-TNF agents are an option [9,12]. In the case of perianal changes, a caesarian section must be considered. In the other cases, including patients with ileo- i colostomias, there is no contraindication for vaginal delivery [11].

There are case studies of pregnant patients with AA amyloidosis caused by FMF [7]. Therefore, it is known that AA amyloidosis by itself is not a contraindication for pregnancy. Two factors are essential. The main factor is good control of the underlying disease, which is sometimes very challenging, because of the toxicity of drugs. The second factor is severe complications

Table I
Laboratory results and treatment.
Wyniki laboratoryjne i leczenie.

	Feb 2008	May2008	Nov 2009	Dec 2010	Dec 2011	Dec 2012	Feb 2014	May 2014	Oct 2014
Laboratory results									
Proteinuria (g/24h)	14.0	9.43	2.8	1.1	1.09	0.28	2.16	n.d.	0.24
Serum albumin (g/L)	28	26	35	29	n.d.	37	23	36	n.d.
Hemoglobin (g/dL)	14.0	15.9	12.1	12.9	12.9	11.3	11.3	12.1	12.4
Serum creatinine (mg/dL)	0.62	0.78	0.83	0.7	0.69	0.78	0.68	0.8	0.9
CRP (mg/L)	7.5	7.48	6	5	<1	2	9	3	4
SAA (mg/L)	n.d.	n.d.	25	12.8	<3,9	5.7	8.2	12.9	18
RR mmHg	90/60	100/70	120/80	120/95	160/90	130/80	150/90	140/80	150/80
Treatment									
Infliximab	IFX	-	-	-	-	-	-	-	-
Methylprednisolone	MTP 32 mg	MTP 32 mg	-	-	-	-	-	-	-
Budesonide	-	-	BUD 3 mg	BUD 3 mg	BUD 3 mg	BUD 3 mg	BUD 3 mg	BUD 3 mg	BUD 3 mg
Azathioprine	-	-	-	AZA100 mg	AZA100 mg	-	-	-	-

Abbreviations; CRP – C-reactive protein, SAA serum amyloid-A, n.d. – not done; Infliximab - IFX, Methylprednisolone –MTP, Budesonide – BUD, Azathioprine - AZA;

of AA amyloidosis. The most severe is nephrotic syndrome with hypoalbuminemia and malnutrition.

AA is observed in between 0.3 – 10.9% of patients with CD [14]. Nowadays, new drugs help to reverse the natural history of AA amyloidosis in CD, therefore pregnancy in AA amyloidosis CD is not impossible. Surprisingly, no case has been described so far.

Conclusion

Pregnancy in a CD patient with AA amyloidosis should be planned in remission of CD symptoms when CRP and SAA are in the normal range. The remission of nephrotic syndrome is very important. Modern therapy of CD gives a chance to achieve remission of AA amyloidosis in patients with chronic inflammatory disease.

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