Cyclic neutropenia complicated by renal AA amyloidosis

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SUMMARY: Metin A, Ersoy F, Tınaztepe K, Beşbaş N, Tezcan İ, Sanal Ö. Cyclic neutropenia complicated by renal AA amyloidosis. Turk J Pediatr 2000; 42: 61-64.

Cyclic neutropenia is a rare disease characterized by regular cyclic fluctuations in the numbers of neutrophils. Patients with the disease suffer from recurrent infections at regular intervals of nearly three weeks. Recently, recombinant human granulocyte colony-stimulating factor (rhG-CSF) was reported to be an effective treatment for this disease. here we describe 17-year-old cyclic neutropenic female patient with a very rare asociation of renal amyloidosis of AA type who was under intermittent rhG-CSF treatment for the previous one and a half years. We conclude that although the disorder is usually benign, reactive amyloidosis may rarely develop in cases who remain untreated for a long period of time. However familial Mediterranean fever (FMF) type II should also be born in mind, particularly in predisposed populations.

Key words: cyclic neutropenia, AA type amyloidosis, renal, childhood.

Cyclic neutropenia is characterized by a history of repetitive infectious complications due to cyclic ossilations in the number of circulating neutrophils. Cyclic neutropenia affects children of both sexes and shows a genetic basis in approximately 25 percent of cases, being most commonly autosomal dominant with variable expression. Between neutropenic periods, patients usually remain free of infection[1].

Although this disorder is usually benign, death from overwhelming infection can occur in as many as 10 percent of affected patients. Clostridium perfringens is reported as one of the more common microorganisms. Some patients may experience clinical improvement as they grow older with the cycles becoming less noticeable and symptoms less conspicuous. The disorder is lifelong and does not predispose to leukemia or aplastic anemia[1].

Here we describe a patient with cyclic neutropenia who developed renal amyloidosis of reactive, AA type under the therapy of recombinant human granulocyte-colony stimulating factor (rhG-CSF).

Case Report

The patient (A.E.), 4.5-year-old female, was referred to hacettepe University Children's Hospital in May 1986 because of an absence of granulocytes on blood count. She had been suffering from recurrent severe aphthous gingivostomatitis, swelling of lips, fever, tonsilitis, otitis and sinusitis since her earliest childhod. She was followed-up by local physicians and treated successfully with antibiotics. The patient was a term, 3400 g product of unrelated parents. She had three healthy older sisters and her family history was unremarkable. On admission she was diagnosed as having pneumonia and otitis media and treated with antibiotics. Routine laboratory examinations revealed a moderate leukopenia (WBC count was 4000 cells/μl) with absolute granulocytopenia with monocytosis (0% neutrophils, 82% lymphocytes, 2% eosinophils and 15% monocytes; platelets were normal). Bone marrow studies revealed an arrest of myelopoiesis at the myelocytic stage with an absence of bands and segmented neutrophils. There were no signs of myelodysplasia and the cellularity of the bone marrow was normal. Her quantitative immunoglobulins, lymphocyte subsets, lymphocyte proliferation with mitogens (phytohemagglutinin and concanavalin A), neutrophil chemotaxis, CH_{50} and nitroblue tetrazolium (NBT) tests were all in normal limits. Cyclic neutropenia was diagnosed by monitoring her neutrophil count two or three

times a week during the frist six weeks following intial presentation. Neutrophil counts were regularly fluctuating with 21-23 day periodicity. neutrophils disappeared from the peripheral blood for three to five days and the patient developed upper and lower respiratory infections, aphthous gingivostomatitis, swelling of the lips and fever during the neutropenic periods. She was then put on prophylactic timethoprim-sulfamethoxazole therapy.

After the diagnosis the patient was followed-up by a local physician with an occasional visit to Hacettepe Children's Hospital (once in 2-3 years) for about ten years.

She was admitted again at 14.5 years of age with the complaints of fever and general malaise in addition to aggravation of the oral symptoms during the neutropenic periods which prevented her from attending school. We therefore started to treat the patient with intermittent subcutaneous rhG-CSF injections of 5 µg/kg/day, just before the initiation of mouth ulcers and/or other infection-related symptoms and signs. no side effects of rhG-CSF were reported and she showed a moderate response to G-CSF therapy clinically with no serious infections except gingivostomatitis of three weekly cycles.

After one year of rhG-CSF therapy, at 16 years of age, she was admitted with pretibial edema without arterial hypertension. Urine examination showed proteinuria when blood chemistry revealed renal function impairment characterized by hypoalbuminemia (total protein: 5.3 g/dl, albumin: 2.5 g/dl), increased serum creatinine (2.7 mg/dl) and decreased glomerular filtration rate (32.5 ml/min/1.73 m^2). Serum C3, C4, IgM and IgA levels were normal while IgG level was moderately decreased (412 mg/dl). Other cellular and humoral immunity tests were within normal limits. There was bilateral kidney enlargement with increased parenchymal echogeneity on abdominal ultrasonography. A renal needle biopsy revealed amyloidosis of AA type; on the suspicion of familial Mediterranean fever (FMF, Type II), colchicine therapy was started. Eight months after the start of the therapy, she still has proteinuria in nephrotic range with deteriorating renal function.

Discussion

Little is known about the pathogenesis of cyclic neutropenia. The cycling of netrophils is accompanied by cycling of other cellular elements, especially the monocytes, and monocyte cycles are opposite to neutrophil cycles, with low neutrophil counts being accompanied by high monocyte counts. The bone marrow exhibits a period of intense myelopoiesis after the period of neutropenia, suggesting the operation of a regulatory negative feed back loop[1]. A well defined etiology has not been established. Sequential bone marrow morphologic changes in patients with cyclic neutropenia and findings after bone marrow transplantation both in humans and in gray collie dogs are consistent with the presence of a defect in granulopoietic progenitor cells. Accumulating evidence indicates that the defect lies either in altered sensitivity of myeloid progenitor cells to growth factors or in defective regulation of granulopoiesis by accessory cells[1].

Until recently the dosage and administration scheme and therapeutic unitilty of rhG-CSF in children with cyclic neutropenia was not well characterized[2-5,7,8]. Most treatment modalities including splenectomy, hormone injections, corticosteroids, intravenous immunoglobulin therapy and nutritional supplements either failed or were marginally successful[1]. In 1989 Hammond et al.[8] reported a benefit with intermittent s.c. rhG-CSF in patients with cyclic neutropenia. The propensity for recurrent mucositis and infection was markedly attenuated. Occurrence of amyloidosis in patients with cyclic neutropenia is rare. As far as we know from a medline survey of 1970-1997, there are at least 270 patients with cyclic neutropenia but only three patients with cyclic neutropenia associated with amyloidosis[9,10]. All previousy reported patients with this combination suffered from frequent infections in association with an inadequate or lack of treatment with G-CSF. In addition, at the time of establishment of the diagnosis of renal amyloidosis, the patients had suffered for almost 20 years, and this is also in agreement with our patient's state. Recently, release of acute-phase serum amyloid-A protein (SAA) during repeated infections/inflammation is suggested to play a major role in the development of secondary amyloidosis, which was also shown in our patient. We suspected the presence of familial Mediterranean fever (FMF) in the presented case, which is commonly complicated by AA type amyloidosis showing renal involvement in untreated cases.

We, therefore, started colchicine therapy, although there was no family or patient history in accordance with FMF. Nevertheless, it cannot be excluded since the Turkish population is especially predisposed and in certain individuals and families amyloidosis is the first and sole clinical manifestation of FMF.

Although effective G-CSF therapy may delay the manifestation of amyloidosis, it can be anticipated that, as it lengthens the survival of the patients, the overall incidence of amyloidosis in cyclic neutropenia might even increase in the future, especially in patients with moderate response to G-CSF.

Unfortunately, it is not presently known why only a few of the patients with cyclic neutropenia are predisposed to develop amyloidosis. Thus it is not possible to recognize the patients at risk in advance. On the other hand, this may be related to the success of the treatment of cyclic neutropenia with G-CSF. To the contrary of that in human beings, in canine cyclic neutropenia there is a high incidence of the development of secondary amyloidosis[11]. This may support the idea that the mechanisms for amyloid deposition are different between human and animal species. Chronic immune activation in various primary immunodeficiencies may also lead to secondary amyloidosis[12,13], but this does not seem sufficient to explain amyloidosis in this case by itself, since the patient did not experience chronic or serious infections. Underlying FMF as another causative predisposing factor cannot be excluded unless a specific mutation in FMF gen is detected[14].

Our patient received G-CSF therapy without the appearance of any complications decribed in relation to its administration, which include exanthema, transient bone pains, arthralgias, arthritis, thrombocytopenia and anemia, leukocytoclastic vasculitis and leukocytoclastic vasculitis complicated by acute renal failure. However, secondary amyloidosis has been suspected to be related to the G-CSF usage in a patient with Felty's syndrome who developed renal AA amyloidosis after prolonged treatment with G-CSF[15].

Gastrointestinal symptoms such as diarrhea and intestinal obtruction were the presenting sings of amyloidosis in the previously described patients of cyclic neutropenia in contrast with the present case who presented with nephropathy[9,10]. This underscores the value of analyzing the urine and renal function in patients with cyclic neutropenia, as the discovery of proteinuria may be the first clue to amyloidosis.

We conclude that although amyloidosis papears to be extremely rare in cyclic neutropenia, it should be taken into account, and urine and renal function tests must be undertaken regularly, at least in cases who remained untreated for a long period of time or who demonstrate a moderate response to G-CSF.

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