HYPERFERRITINEMIA IN A KIDNEY TRANSPLANT RECIPIENT

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SUMMARY – The principal iron storage protein is ferritin, which is primarily present in cytoplasm. The most common cause of hyperferritinemia is iron overload, which is either primary or secondary. Hyperferritinemia is commonly found in patients with chronic kidney disease regardless of their hemoglobin level and is often considered to be related to chronic inflammatory status as well as malnutrition and neoplasias. We present a case of a kidney transplant patient that developed severe hyperferritinemia associated with liver dysfunction. In our patient, high hyperferritinemia was detected a year after transplantation, when she had no signs of inflammation. Malignancies, chronic viral hepatitis, and chronic inflammatory disease were also excluded as the causes of hyperferritinemia. Since high serum ferritin levels were combined with increased transferrin saturation and mildly elevated plasma iron concentrations, we presume that the most probable cause of hyperferritinemia in our patient was iron overload.

Key words: *Kidney transplantation; Chronic kidney failure; Hyperferritinemia; Iron overload; Case report*

Introduction

The principal iron storage protein is ferritin, which is primarily present in cytoplasm. It is composed of 24 subunits that are of two different types, heavy and light chains, MW 18000 Da[1,2]. The main role of ferritin is the regulation of iron metabolism either for the synthesis of hemoglobin or for the oxidation of highly toxic Fe (II) into Fe (III)[3]. Ferritin synthesis is regulated by intracellular iron concentration[2,4]. The most common cause of hyperferritinemia is iron overload, which is either primary or secondary. Hereditary hemochromatosis (HH) is the most often cause of primary iron overload. HH is a genetically heterogeneous disease that is caused by mutations located on the HFE gene; the most common ones are termed C282Y and H63D[5].

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Secondary iron overload results from excessive intake of iron from multiple blood transfusions, parenteral iron administration, dietary intake, or iron supplements. It can also occur in patients who have chronic disorders of erythropoiesis or hemolytic anemias[5].

Hyperferritinemia in the absence of iron overload may occur in certain liver diseases such as chronic viral hepatitis[6], during episodes of inflammation, since ferritin is an acute phase reactant[7], and in inflammatory diseases (e.g., rheumatoid arthritis and hemophagocytic lymphohistiocytosis). Obesity and malignancy can also raise plasma ferritin concentration[8]. Hyperferritinemia is commonly found in patients with chronic kidney disease (CKD) regardless of their hemoglobin level, and is often considered to be related to chronic inflammatory status as well as malnutrition and neoplasias[9]. Patients with CKD under different forms of renal replacement therapy are also at a risk of developing secondary iron overload for two reasons. First, before erythropoietin therapy for correction of renal anemia they frequently receive blood trans-

fusions. Second, from the introduction of treatment with erythropoiesis-stimulating agents these patients routinely receive iron supplementation for successful treatment of renal anemia[10].

We present a case of a kidney transplant patient that developed severe hyperferritinemia associated with liver dysfunction.

Case Report

A 55-year-old woman with end-stage renal disease due to polycystic kidney disease, who had been treated with hemodialysis (HD) for 11 years, received a renal allograft from a deceased donor at age 51. As part of her HD treatment, she had been administered iron i.v. during a 6.5-year period. On one occasion, she received blood transfusion. Laboratory findings at the time of kidney transplantation showed normal liver function (AST 20 U/L, ALT 39 U/L). The kidney transplantation was performed and she was treated with cyclosporine, mycophenolate mofetil and prednisone.

Graft function after transplantation was normal and remained stable throughout the 4-year follow-up period (mean creatinine value 93.3±5.0 μg/L). No episodes of graft rejection were noted during that time. On day 5 of transplantation, an increase in liver enzymes (ALT 67 U/L, AST 29 U/L, GGT 32 U/L) was noted, reaching maximum on day 7 of transplantation, and remained increased throughout the follow-up period (Fig. 1). A year after transplantation, severe hyperferritinemia (ferritin 4195 μg/L; normal range for female 20-120 μg/L) combined with transferrin saturation (TSAT) of 75% and a mild increase in serum iron and TIBC (serum Fe 39 μmol/L, TIBC 52 μmol/L) was detected. During the next three years, ferritin levels and TSAT remained high (mean ferritin 3399.6±19.6 μg/L, mean TSAT 74.6±1.8%, mean serum Fe 34.5±1.6 μg/L, mean TIBC 46.3±1.8 μmol/L) (Fig. 1). Therapeutic venepunctures were started two years after detection of hyperferritinemia.

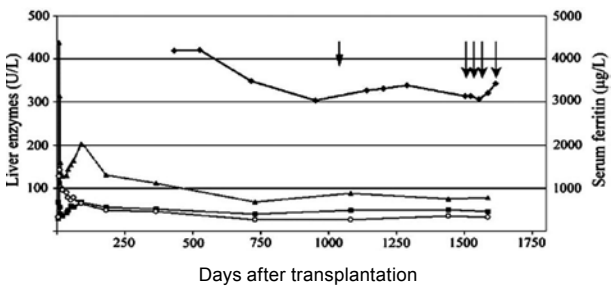

Fig. 1. Changes in serum liver enzyme levels (triangles indicate levels of ALT, squares levels of AST, and circles levels of GGT); serum ferritin concentrations during the follow-up period are shown by rhombi. Black arrow indicates the beginning of gastroenterologic involvement. Grey arrows show the time of therapeutic bloodletting treatment.

Ultrasonography (US) of the abdomen showed enlarged liver with multiple cystic formations. Abdominal multislice computed tomography (MSCT) showed multiple cystic formations, increased parenchymal density and an accessory spleen.

Bone marrow aspiration showed increased white to red cell line ratio (5.5:1). Erythropoiesis was slightly depressed, mature, with low percentage of megaloblastoid cells. Cytomorphological appearance of peripheral blood smear was within the normal range.

Genetic analysis for hereditary hemochromatosis (C282Y, H63D and S65C) was negative. Both hepatitis B virus surface antigen and C virus antibody were negative, as well as cytomegalovirus (CMV) antigenemia. Autoimmune and metabolic disease, tumors, and hemolytic anemia were excluded as the reasons of hepatic lesion. Due to multiple liver cysts, liver biopsy was not performed.

Discussion

It is well known that liver impairment may occur after kidney transplantation[11]. The possible etiologies for liver dysfunction after renal transplantation include drug toxicity (immunosuppressive and non-immunosuppressive agents)[12,13], viral activity (hepatits B, hepatitis C, CMV and other hepatotoxic viruses), vascular lesion and sepsis[12]. Our patient showed signs of severe hyperferritinemia and early liver impairment after transplantation. Since she had cystic formations in the liver prior to transplantation as part of her primary renal disease (polycystosis) and normal levels of liver enzymes, we presume that the liver impairment was not of that source. The most probable cause of liver impairment was cyclosporine toxicity. Cyclosporine and prednisone therapy have been associated with hepatotoxic episodes that were usually self-limited, and generally occurred during the very

early posttransplant period[13]. Hyperferritinemia may be found in patients with CKD regardless of their hemoglobin level and is often considered to be related to chronic inflammation, malnutrition and neoplasias[9]. In our patient, high hyperferritinemia was detected a year after transplantation, without signs of inflammation. During the follow-up period, neoplasias, chronic viral hepatitis and chronic inflammatory disease were also excluded as the reasons of hyperferritinemia. Since high serum ferritin levels were combined with increased TSAT and mildly elevated plasma iron concentrations, we presume that the most probable cause of hyperferritinemia in our patient was iron overload. In the study of iron overload in kidney transplantation, it was shown that about 36% of such patients also had *HFE* mutations[10]. In our case, *HFE* mutations for hereditary hemochromatosis were negative, and parameters showing iron overload and liver impairment remained increased throughout the follow-up period, unlike the study group, thus indicating that our patient was not in this class. Alternatively, in a case report[14], liver dysfunction was assigned to hemosiderosis in a renal transplant recipient, due to blood transfusions and iron replacement therapy prior to kidney transplantation; our patient might be a candidate for such assignment, however, liver biopsy to confirm this presumption was contraindicated in our patient.

This case is presented to emphasize the importance of iron store assessment in patients with chronic kidney disease prior to initiating therapy. Both TSAT and serum ferritin should be considered. In hemodialysis patients, absolute iron deficiency is considered when TSAT is <20% and serum ferritin concentration is less than 200 μg/L. Functional deficiency is associated with TSAT ≤20% and serum ferritin higher than 200 μg/L, and is characterized by the presence of adequate iron stores but inability to sufficiently mobilize iron when erythropoiesis is stimulated by an erythropoietic stimulating agent[15]. In both cases, a sufficient amount of iron to correct iron deficiency should be administered[16], but the administration of intravenous iron should be individually assessed in patients with ferritin levels above 500 μg/L and anemia. In patients with serum concentration above 500 μg/L and/or TSAT above 50%, iron should be administered with caution due to the probability of iron overload. Iron therapy and erythropoietic stimulating agents should be administered in hemodialysis patients to achieve and maintain target hemoglobin levels between 110 and 120 g/L in accordance with the K/DOQI guidelines[16].

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Sažetak

HIPERFERITINEMIJA U BOLESNIKA S PRESATKOM BUBREGA

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Feritin je glavni protein za skladištenje željeza i prvenstveno je prisutan u citoplazmi. Najčešći uzrok hiperferitinemije je preopterećenje željezom, koje može biti primarno ili sekundarno. Hiperferitinemija se često nalazi u bolesnika s kroničnom bubrežnom bolesti bez obzira na razinu njihovog hemoglobina i smatra se da je povezana s kroničnom upalom, pothranjenošću i novotvorinama. Prikazujemo slučaj bolesnice s transplantiranim bubregom u koje se razvila teška hiperferitinemija povezana s jetrenom disfunkcijom. U naše bolesnice hiperferitinemija je otkrivena godinu dana nakon transplantacije, kada u nje nije bilo znakova upale. Zloćudne bolesti, kronični virusni hepatits i kronična upalna bolest su također isključeni kao uzroci hiperferitinemije. Kako je visoka koncentracija feritina bila udružena s povišenom zasićenošću transferina i umjereno povišenom koncentracijom željeza u plazmi, pretpostavljamo da je najvjerojatniji uzrok hiperferitinemije bilo preopterećenje željezom.

Ključne riječi: *Transplantacija bubrega; Bubrežna insuficijencija, kronična; Hiperferitinemija; Željezo, opterećenje; Prikaz slučaja*