Extreme hypercalcemia in a kidney transplant recipient

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Abstract

Post-transplant hypercalcemia is a major problem in renal transplant recipients, which may negatively affect both graft and patient survival. In this paper, we present a 66-year-old male kidney transplant recipient, who was admitted to our clinic with symptoms of fever, nausea, vomiting and lethargy. Laboratory data showed good renal function; however, a serum calcium level of 22.1 mg/dL. The patient was treated by isotonic saline together with furosemide and methylprednisolone. Because of treatment resistance, subcutaneous calcitonin and ibandronate were added to the treatment protocol as well. Since all these medications were not effective, hemodialysis with low-calcium (1.25 mmol/L) dialysate was applied for three consecutive days, which resulted in normalization of serum calcium. Several investigations were carried out for diagnosing the underlying etiology. Positron-emission tomography (PET)/CT revealed a strong diffuse uptake of FDG in the bones and spleen. A bone marrow biopsy showed diffuse interstitial infiltration of CD20 + neoplastic B cells and, thus, post transplant lymphoproliferative disease (PTLD) was diagnosed. Tacrolimus was switched to everolimus, mycophenolate mofetil was stopped, while treatment with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) was initiated. Despite all therapeutic interventions, the patient died of septic shock in the intensive care unit on the 10th day of emergency service admission. Importance of hemodialysis as an emergent treatment modality in extreme hypercalcemia, and unfavorable course of PTLD were underlined.

Keywords Hypercalcemia · Kidney transplantation · Hemodialysis · Lymphoproliferative disorders

Introduction

Post-transplant hypercalcemia is a major problem in renal transplant recipients, which may negatively affect both graft and patient survival [1, 2]. Its incidence may rise up to 59% in the early post-transplant period, while this high figure comes back to the normal range after several months [3–7]. Underlying etiology include, but are not limited to hyperparathyroidism, malignancy, hyperthyroidism, acromegaly, adrenal insufficiency, tuberculosis, sarcoidosis and some medications [estrogens, lithium, thiazide diuretics, excess vitamin D or vitamin A ingestion] [1, 2, 6, 7]. Symptoms of hypercalcemia range from an asymptomatic laboratory abnormality to a life-threatening medical emergency. Usually, the first signs and symptoms are noted in the nervous/musculoskeletal system causing fatigue, muscle weakness, impaired mental concentration or physical sluggishness. When serum calcium reaches a critical level [> 14 mg/dL], coma and death may occur [8–10].

Hypercalcemic crisis is characterized by severe hypercalcemia in association with organ dysfunction. Among

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the above cited etiologies of hypercalcemia; malignancies (70%), hyperparathyroidism (20%) and other conditions (10%) are more frequently associated with hypercalcemic crisis [10] in renal transplant recipients. To the best of our knowledge, malignancy-associated hypercalcemic crisis after kidney transplantation has not been reported before. Here, we present a case of a kidney transplant recipient with hypercalcemic crisis due to posttransplant lymphoproliferative disorder (PTLD).

Case report

A 66-year-old male kidney transplant recipient was admitted to the transplant clinic with symptoms of high fever, nausea, vomiting, bone pain, loss of appetite and lethargy. He was diagnosed with membranous nephropathy 9 years ago; past medical history and family history was not significant. The disease progressed to end stage renal disease within a 6-month period; hence he had a living-donor transplantation surgery from his brother. Pre-transplant viral serology was negative for both donor and recipient regarding hepatitis B, hepatitis C and human immunodeficiency virus while seropositivity was noted for *Epstein Barr virus*, *Cytomegalovirus* and *Varicella Zoster virus*, each.

Transplantation operation was uneventful. Antithymocytic globulin (2 mg/kg per 8 days: total dose 16 mg/kg) was administered for induction therapy and immunosuppressive regimen included tacrolimus, mycophenolate mofetil and prednisolone. Posttransplant infection prophylaxis included valganciclovir and fluconazole for 3 months; and trimethoprim sulfamethoxazole for 1 year.

Posttransplant course was uneventful for 6 years. Most recent laboratory tests were measured a month ago before admission, demonstrated serum creatinine: 1.2 mg/dL, calcium: 9.8 mg/dL, phosphorus: 3.8 mg/dL, high-sensitivity C-reactive protein: 1.2 mg/L and intact parathyroid hormone (iPTH) level: 34 pg/mL. However, serum LDH levels were not provided, since this parameter was not registered in the medical records. Any medications, which might affect calcaemia had not been used.

On physical examination, the patient was confused and hypotonic. Temperature was 37.5 °C, blood pressure was 80/50 mmHg; however, other findings were unremarkable. Laboratory data showed serum creatinine: 1.8 mg/dL, calcium: 22.1 mg/dL, ionized calcium: 2.137 mmol/L, phosphorus: 6.8 mg/dL, iPTH: 14 pg/mL, 25-hydroxyvitamin D concentration: 18.5 ng/mL, lactate dehydrogenase: 750 U/L, total protein: 5.5 gr/dL and albumin: 3.5 g/dL.

The patient was immediately treated by isotonic saline (200 mL/kg per day) together with IV bolus furosemide 120 mg and methylprednisolone 40 mg. 3 h later, subcutaneous calcitonin was initiated 4 IU/kg, every 6 h, in addition to

a single dose of IV ibandronate 4 mg. Since this regimen did not decrease serum calcium over a 6-h period, hemodialysis with a low-calcium (1.25 mmol/L) dialysate was applied for three consecutive days.

During this period, isotonic saline, furosemide and methylprednisolone were administered, as well. Course of calcaemia and response to various therapeutic interventions are shown in Fig. 1.

Regarding to diagnostic studies; Positron-emission tomography (PET)/CT revealed a strong diffuse uptake of FDG in the bones and spleen (Fig. 2). A bone marrow biopsy revealed diffuse infiltration of a large lymphoid cells. Immunohistochemically neoplastic cells were positive for CD20 and were negative for CD3, CD5, cyclin D1, CD10, bcl6 and Tdt. MUM1 was focally expressed. Neoplastic cells revealed high proliferative index with Ki67 (90%). Morphological and immunohistochemical findings were consistent with diffuse large B cell lymphoma (Fig. 3). Immunohistochemistry for EBV-LMP and in situ hybridization for Epstein-Barr virus encoded RNA (EBER) were negative in neoplastic cells.

Tacrolimus was switched to everolimus, mycophenolate mofetil was stopped, while treatment with R-CHOP (600 mg rituximab, 1320 mg cyclophosphamide, 88 mg doxorubicin, 2 mg vincristine, and 5 mg prednisone), fluconazole prophylaxis against fungal infections and trimethoprim and sulfamethoxazole against *Pneumocystis jiroveci* infection were initiated and the patient was discharged in a good clinical condition 52 days after hospital admission. His serum creatinine was 0.5 mg/dl and serum calcium level was 8.6 mg/dl during discharge. His chemotherapy was continued in the outpatient clinical basis.

40 days after discharge, the patient was admitted to the emergency service with fever and cough. On physical examination, crackles were heard in the base of both

Fig. 1 Course of serum calcium levels and response to various treatment strategies

Fig. 2 Positron-emission tomography with 18F-fluorodeoxyglucose revealed a strong diffuse uptake of FDG in the bones and spleen

lungs. Temperature was 38.5 °C and blood pressure was 125/75 mmHg. Severe hypoxemia (SO_2 :80%) was found in arterial blood gas analysis. Chest X-ray and thorax computed

tomography examinations revealed bilateral reticulonodular infiltrates. Laboratory data showed, serum CRP: 267 mg/L, lactate dehydrogenase: 206 U/L, albumin: 2.2 g/dL creatinine: 0.9 mg/dL, calcium: 7.3 mg/dL and phosphorus: 2.5 mg/dL. Thus, bacterial pneumonia was diagnosed and empirical treatment with meropenem and oxygen therapy were initiated.

Fever and hypoxemia persisted despite antibiotic treatment, bronchoscopy was performed because of hemoculture, and sputum culture yielded no growth. Bilateral pulmonary consolidation and diffuse infiltrates were seen in thorax computed tomography (Fig. 4). *Acinetobacter baumannii* was detected in bronchoalveolar lavage culture specimen and colistin was added to the initial antimicrobial regimen. *Pneumocystis jiroveci* pneumonia was excluded because of negative polymerase chain reaction results in bronchoalveolar lavage specimen. Since the patient's general condition deteriorated and hypotension developed, dobutamine was initiated and he was transferred to the intensive care unit. The patient died of septic shock in the intensive care unit on the 10th day of emergency service admission.

Discussion

Hypercalcemia is the most common mineral disorder in kidney transplant recipients [5]. Its prevalence ranges 4.5–58.6% [5, 10]. This wide range can be explained by several factors; most importantly older studies reported higher prevalence of hypercalcemia, because of less efficient control of PTH [3]. Hypercalcemia has been divided into three severity categories, i.e., (1) mild (< 12 mg/dL), (2) moderate (11–14 mg/dL) and (3) severe (> 14 mg/dL) [11]. Severe hypercalcemia is not frequent in clinical practice: highest

Fig. 3 **a** Bone marrow biopsy revealed diffuse interstitial lymphoid infiltration (H&E, 20× magnification). **b** At high power view large, atypical lymphocytes with centroblastic features (H&E, 40× magni-

fication). **c** Neoplastic cells were reactive with CD20. **d** Neoplastic cells have high proliferation index with Ki67

Fig. 4 Thorax computed tomography demonstrates bilateral pulmonary consolidation and diffuse infiltrates

serum level of calcium has been reported as 30 mg/dL in the nontransplant population [12] and 13.6 mg/dL in the renal transplant population [13]. In our case, the serum Ca level was 22.1 mg/dL and to the best of our knowledge, this is the highest calcemia in a transplant population so far. Since our patient was not using any medications, which may cause hypercalcemia we can only speculate about this excess level, which is late admittance of the patient, after being complicated by B cell lymphoma.

Pseudohypercalcemia [elevation of total plasma calcium levels conversely than ionized calcium levels] might be considered assuming that this level of serum calcium may not be compatible with life. Indeed, pseudohypercalcemia has been reported in malignancies such as Waldenström's macroglobulinemia and multiple myeloma [15]. However, in our case serum total protein level was normal and a serum protein electrophoresis did not reveal any abnormalities.

Post-transplant lymphoproliferative disorder is the most serious and potentially fatal malignancy occurring in the setting of kidney transplantation. Prolonged high doses of immunosuppression and EBV seropositive donor and seronegative recipient are the main risk factors for development of PTLTD. In our case, modest dosages of ATG were administered as induction therapy, whereas EBV seropositivity did not reveal any specific risk for PTLTD development [14].

Treatment of hypercalcemic crisis is an emergency since this problem may cause fatalities [8–10]. Therefore, we applied saline, furosemide and glucocorticoids to restore hypovolemia and increase calciuresis [10, 11]. Since this treatment was not effective, calcitonin and bisphosphonates were added to the treatment regimen. However, these medications did not work as well; therefore, hemodialysis was applied as a rescue treatment [5]. Resistance to the antihypercalcemic medications

is obscure in our case; however, we speculate that advanced lymphoma may be responsible for this unresponsiveness [12].

Regarding to the ultimate outcome, severe posttransplant hypercalcemia may be associated with poor prognosis [1]. Mostly, median survival is less than 1 year after diagnosis [12, 15]. Higher age, advanced disease and elevated lactate dehydrogenase levels all have been suggested as poor prognostic indicators [15]. Unfortunately, our case was not an exception and he died within 4 months after the diagnosis.

Bone marrow infiltration of diffuse large B cell lymphoma indicates stage IV disease, which is associated with a worse outcome. The frequency of bone marrow infiltration by diffuse large B cell lymphoma varies 10–60% [16]. It might show paratrabeular, diffuse, interstitial, mixed or nodular patterns [16]. Diffuse pattern is the most common form and often related to chemotherapy resistance [16]. Hypercalcemia typically occurs 15% of lymphoma patients during the course of their disease and is usually seen in tumors that are more aggressive; however, severe hypercalcemia in diffuse large B cell lymphoma at the time of diagnosis is very rare (less than 3% of cases) [17]. In our case, bone marrow infiltration showed diffuse pattern and to the best of our knowledge, this is the first case described in kidney transplant recipient, which present severe hypercalcemia at the time of diagnosis due to diffuse large B cell lymphoma.

To conclude, PTLTD is a serious complication in renal transplant recipients, which may cause morbidity and mortality. Although rare, hypercalcemic crisis can be seen in these patients and hemodialysis should always be considered as a rescue intervention at least in early phase of hypercalcemic crisis.

Author contributions ED, CK and HY performed the collection and interpretation of the data. CK prepared the manuscript. ED, HY, SM, BS and MSS critically revised the paper. All authors read and approved the final version.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Written informed consent was obtained from the patient's parents for publication of this case report and accompanying images. A copy of the written consent may be requested for review from the corresponding author.

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