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CASE REPORT

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Atypical presentation of PJP: hypercalcemia and kidney injury in an allogeneic stem cell transplant recipient

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Abstract

Background Pneumocystis jirovecii pneumonia (PJP) is an opportunistic infection that primarily affects immunocompromised individuals. Typical symptoms of PJP include the subacute onset of dyspnea, nonproductive cough, and low-grade fever. In hematology patients, particularly those who are allogeneic stem cell transplant recipients, the disease often presents with a more aggressive clinical course. While hypercalcemia has been documented as a manifestation of PJP in some solid organ transplant recipients, it has not been reported in hematology or stem cell transplant patients.

Case presentation Here, we present a case of PJP in a 56-year-old male allogeneic stem cell transplant recipient, who developed hypercalcemia and renal failure during the late post-transplant period. The patient had a history of allogeneic stem cell transplantation due to acute myeloid leukemia. He presented with symptoms of fatigue and weakness. Laboratory tests revealed hypercalcemia (13.8 mg/dL) and elevated serum creatinine levels (2.3 mg/dL). The patient was hospitalized, and despite initial treatment with hydration and furosemide, the hypercalcemia persisted, leading to the administration of denosumab. During follow-up, hypoxia was detected, and a chest CT scan revealed mosaic attenuation and ground-glass opacities. Bronchoscopy was performed, and PCR testing confirmed the presence of Pneumocystis jirovecii. Other causes of hypercalcemia were ruled out, with PTH measured at 13.8 pg/mL (normal range 15–65 pg/mL), albumin at 3.71 g/dL, 1.25-dihydroxy vitamin D3 at 96 ng/dL (normal range 26–95 ng/dL), and 25-hydroxy vitamin D at 32.5 ng/mL (normal range 20–40 ng/mL). A PET-CT scan demonstrated no pathological FDG uptake, with the exception of findings suggestive of a pulmonary infection. Following treatment with trimethoprim-sulfamethoxazole and denosumab, the patient's hypercalcemia and infection resolved.

Conclusions Although rare, PJP can present with hypercalcemia and kidney injury in allogeneic stem cell transplant recipients. Early diagnosis and treatment can improve both PJP and hypercalcemia.

Keywords Pneumocystis jirovecii, Pneumonia, Hypercalcemia, Allogeneic stem cell transplantation

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Background

Pneumocystis jirovecii pneumonia (PJP) is an opportunistic infection caused by the fungus P. jirovecii, commonly affecting immunocompromised individuals, such as those with HIV, organ transplant recipients, or patients who have undergone allogeneic stem cell transplants. Primary prophylaxis is typically recommended for this high-risk group [1, 2].

Notably, patients can develop the condition after discontinuing trimethoprim-sulfamethoxazole prophylaxis or even while receiving prophylactic treatment, therefore it should still be considered in the differential diagnosis if there is a high clinical suspicion [3].

Typical symptoms of PJP include the subacute onset of dyspnea, nonproductive cough, and low-grade fever. Compared to HIV-positive patients, who tend to have a more indolent clinical course, hematology patients with PJP often experience a sudden onset of hypoxic respiratory failure and dyspnea, frequently requiring intensive care. Hypercalcemia is not commonly associated with PJP; however, it has been reported in many cases involving solid organ transplant recipients, particularly those who have undergone kidney transplants [2, 4].

Here, we present a case of PJP in an allogeneic stem cell transplant patient who developed hypercalcemia and renal failure in the late period of transplantation. Denosumab was used in the management of hypercalcemia. According to our literature review, this is the first reported case of PJP presenting with hypercalcemia and kidney injury in allogeneic stem cell transplant recipient.

Case presentation

A 56-year-old male patient with known diagnoses of diabetes mellitus and acute myeloid leukemia (AML) in remission underwent an allogeneic stem cell transplant (allo-HSCT) from a 9/10 HLA-matched unrelated donor, using a myeloablative conditioning regimen (busulfan and fludarabine). There was major and minor blood group incompatibility between the donor and the recipient. Post-transplant cyclophosphamide, cyclosporine, and mycophenolate mofetil were used for graft-versus-host disease (GVHD) prophylaxis. Early post-transplant complications included febrile neutropenia and mucositis. Neutrophil engraftment occurred on day+16, platelet engraftment on day+18, and the patient was discharged on day+24.

The patient was maintained on cyclosporine, mycophenolate mofetil (discontinued on day+35), valacyclovir (500 mg BID), trimethoprim-sulfamethoxazole (800/160 mg, three times a week), and ursodeoxycholic acid (500 mg BID for the first 90 days). Due to ongoing severe anemia, the patient received one unit of erythrocyte suspension weekly. Full donor chimerism was detected at 1 and 3 months, but a bone marrow biopsy at 3 months revealed pure red cell aplasia on a background of mildly hypocellular bone marrow. Immunosuppressive therapy was discontinued in the fourth month, followed by steroid treatment (prednisolone 1 mg/kg for a week) and then rituximab (375 mg/m^2, weekly for four doses) due to a lack of response. The patient's erythrocyte transfusion requirement gradually decreased.

Prophylactic trimethoprim-sulfamethoxazole was discontinued 8 months after transplantation when the lymphocyte count reached 1040/mm^3. The patient was monitored with hemoglobin levels between 7 and 8 g/dL without the need for transfusions.

In the eleventh month post-transplant (day 325 of transplant), the patient presented with fatigue and weakness for one week. Physical examination revealed no signs of infection or GVHD. Laboratory tests showed hypercalcemia (13.8 mg/dL) and elevated creatinine (2.3 mg/dL), leading to hospitalization. Additional tests revealed WBC 9930/mm^3, lymphocytes 510/mm^3, Hb 7.5 g/dL, platelets 515,000/mm^3, CRP 5 mg/L, LDH 208 U/L (normal range 135–225 U/L), plasma CMV-DNA PCR negative (negative < copies/mL), serum galactomannan 0.150 (normal < 0.5), PTH 13.8 pg/mL (normal range 15–65 pg/ml), albumin 3.71 g/dL, 1.25-dihydroxy vitamin D3 96 ng/dL (normal range 26–95 ng/dL), and 25-hydroxy vitamin D 32.5 ng/mL (normal range 20–40 ng/mL).

Despite intravenous hydration and furosemide treatment, there was no improvement in calcium and creatinine levels. Creatinine clearance was calculated as 38 ml/min. Denosumab (120 mg) was administered on the third day of hospitalization. During follow-up, the patient remained asymptomatic except for subfebrile fever (max fever 37.6 °C) and low oxygen saturation levels (89–90%) on room air. Chest CT revealed widespread mosaic attenuation and ground-glass opacities suggestive of viral pneumonia (Fig. 1). Bronchoscopy and subsequent PCR testing confirmed Pneumocystis jirovecii pneumonia (PJP). Additionally, bronchoalveolar lavage (BAL) for CMV PCR and viral respiratory panel (including Influenza A, Influenza B, Coronavirus 229E, OC43, NL63, HKU1, Parainfluenza 1, 2, 3, 4, Metapneumovirus, Rhinovirus, RSV, Bocavirus, Enterovirus, Parechovirus, Adenovirus, Legionella pneumophila, Mycoplasma pneumoniae, Chlamydia pneumoniae, Haemophilus influenzae, Streptococcus pneumoniae, Bordetella pertussis, Influenza A subtype H1N1/2009, H1, H3), tuberculosis PCR and galactomannan (0.1) were negative.

The patient was started on treatment-dose trimethoprim-sulfamethoxazole and prednisolone (40 mg, once daily for four days). Due to low IgG levels (327 mg/dL), IVIG (0.4 g/kg) was also administered. PET-CT was performed to rule out malignancies, showing areas of increased metabolic activity with ground-glass opacities in both lungs (suggestive of infection). No pathological

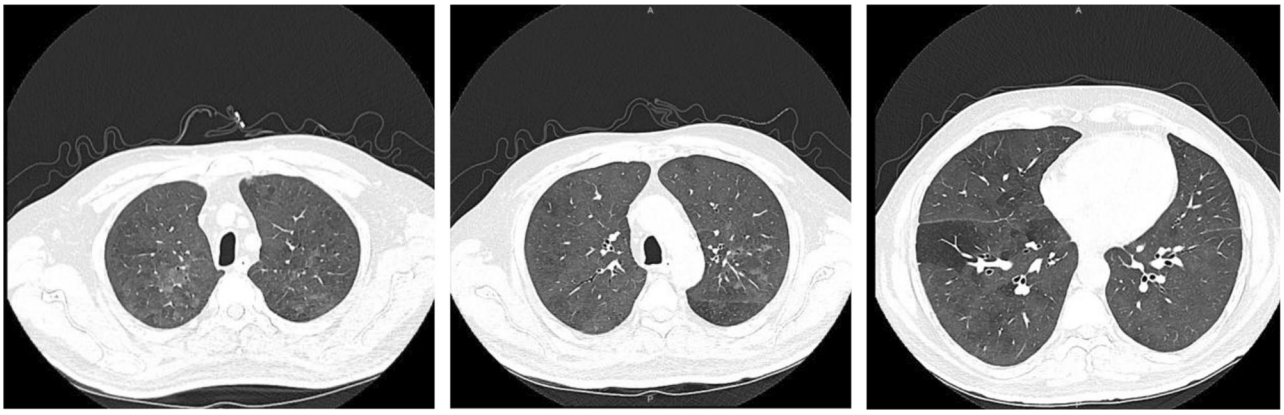

Fig. 1 Mosaic attenuation and ground-glass opacities in Chest CT

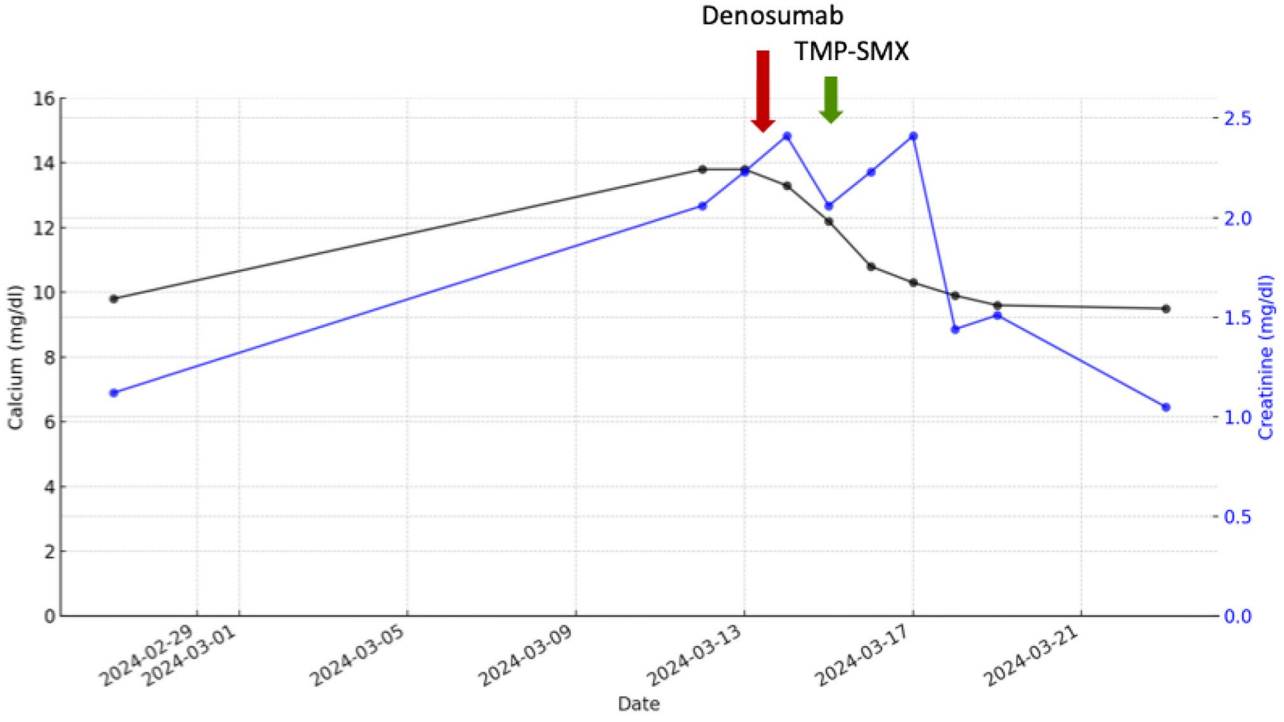

Fig. 2 Calcium and creatinine response to Trimethoprim-Sulfamethoxazole (TMP-SMX) and denosumab

uptake indicative of malignant involvement was observed in other body areas.

After one week of treatment, calcium (9.2 mg/dL), creatinine (0.96 mg/dL) (Fig. 2), and oxygen saturation on room air normalized, and the patient was discharged with a continuation of oral treatment for three weeks.

At the 18-month follow-up post-transplant, the patient remained without additional complications, and the latest tests showed WBC 6670/mm3, lymphocytes 1140/mm3, Hb 9.6 g/dL, platelets 472,000/mm3, calcium 9.54 mg/dL, and creatinine 1.04 mg/dL.

Discussion and conclusions

We present a case of an allogeneic stem cell transplant recipient who developed hypercalcemia and acute kidney injury in the late post-transplant period, with no symptoms other than fatigue, associated with Pneumocystis jirovecii pneumonia (PJP). After the failure of hydration and furosemide to resolve the hypercalcemia, a single dose of denosumab was administered.

The CIBMTR analysis of Pneumocystis jirovecii pneumonia (PJP) in HSCT patients reported an incidence of 0.63% in allogeneic (allo) recipients. The highest risk period for PJP is considered to be from day 80 to day 270 post-HSCT, with a median time to development of 120 days. Risk factors for PJP include lymphopenia, T-cell

dysfunction, immunosuppression, GVHD, and HLA mismatch [5].

Our patient, who underwent a mismatched unrelated allo-HSCT, was not receiving immunosuppressive therapy (IST) and had no history of GVHD at 11 months post-transplant. However, it was later discovered that the absolute lymphocyte count, which had normalized by month 8, had decreased again, likely due to the delayed effects of rituximab.

PJP typically presents with an abrupt onset, marked by symptoms such as fever, non-productive cough, dyspnea, and diffuse interstitial pneumonia. The disease typically progresses rapidly, especially in cases of non-HIV-associated PJP, with the average time from symptom onset to diagnosis being just a few days. In allogeneic stem cell transplant (ASCT) recipients, PJP may present with an even more sudden onset, leading to rapid clinical deterioration and frequently necessitating admission to the intensive care unit [6–8].

Hamroun et al. reported that hypercalcemia was detected at the time of diagnosis in 18 out of 49 (37%) kidney transplant patients with PJP. They noted that cases with hypercalcemia had a more indolent clinical course and presented with febrile dyspnea [9]. While hypercalcemia has been reported in liver transplant patients and other immunosuppressed patients with PJP in case reports, we found no cases in the literature of PJP presenting with hypercalcemia in hematology or stem cell transplant patients [10–13].

It has been suggested that the hypercalcemia observed in patients with PJP is due to the extra-renal production of 1,25-dihydroxyvitamin D as a result of a granulomatous response to Pneumocystis [12, 13]. Previous research has documented temporary increases in 1,25-dihydroxyvitamin D levels associated with hypercalcemia in PJP cases [13, 14]. Similar to other granulomatous diseases, such as tuberculosis and sarcoidosis, granulomatous PJP may lead to the endogenous production of 1-alpha-hydroxylase by activated macrophages. This enzyme catalyzes the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, which in turn enhances bone resorption and intestinal calcium absorption. The resolution of mineral metabolism abnormalities following infection treatment further supports the involvement of PJP in the pathogenesis of hypercalcemia [12–14]. The frequent occurrence of hypercalcemia in PJP patients, coupled with the timing of its onset and resolution in relation to the infection, indicates a direct connection facilitated by increased production of 1,25-dihydroxyvitamin D [14–16].

Supporting this hypothesis, we observed a slight elevation in 1,25-dihydroxyvitamin D levels in our case, accompanied by suppressed PTH and normal 25-hydroxyvitamin D levels. Given the rapid progression of PJP infection in hematopoietic transplant patients, likely due to their profound immunosuppression, we suggest that there may be insufficient time for granuloma formation, 1,25-dihydroxyvitamin D production, and, consequently, the development of hypercalcemia.

In a pediatric case with refractory hypercalcemia despite treatment with TMP-SMX, hypercalcemia was resolved following the administration of denosumab [17]. Another case involved the use of pamidronate therapy [18]. In the review by Hamroun et al., it was noted that in adult renal transplant recipients, bisphosphonate therapy was administered when hypercalcemia was identified prior to the diagnosis of PJP. However, in the majority of cases, the management of PJP resulted in the gradual normalization of hypercalcemia [9]. In our case, despite early hydration and furosemide treatment, hypercalcemia and acute kidney injury persisted, leading to the administration of denosumab, which subsequently normalized calcium and creatinine levels.

According to our literature review, this case represents a rare instance of PJP manifesting with hypercalcemia and acute kidney injury in an allogeneic stem cell transplant recipient, occurring eleven months post-transplant and six months after rituximab treatment for pure red cell aplasia. Although rare, PJP can present with hypercalcemia and kidney injury in allogeneic stem cell transplant recipients. Early diagnosis and treatment can improve both PJP and hypercalcemia.

Abbreviations

allo-HSCT	Allogeneic Hematopoietic Stem Cell Transplant
AML	Acute Myeloid Leukemia
CMV	Cytomegalovirus
CRP	C-Reactive Protein
GVHD	Graft-Versus-Host Disease
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
IST	Immunosuppressive Therapy
IVIG	Intravenous Immunoglobulin
LDH	Lactate Dehydrogenase
PJP	Pneumocystis jirovecii pneumonia
PCR	Polymerase Chain Reaction
PET-CT	Positron Emission Tomography–Computed Tomography
PJP	Pneumocystis jirovecii pneumonia
PTH	Parathyroid Hormone
RSV	Respiratory Syncytial Virus
TMP-SMX	Trimethoprim-Sulfamethoxazole

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Author contributions
Y.C.Ö., H.S., M.G.T., and H.S.B. were responsible for writing the main manuscript. S.M. and Ö.G.S. collected, analyzed, and interpreted the data. S.Y.K. prepared the figures. H.S.B. and L.K. assessed the patient. All authors revised the manuscript critically for important intellectual content, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work. Additionally, L.K., as the corresponding author, had overall supervision and coordination responsibilities for the study, ensuring its integrity and accuracy.

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Data availability
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The publication of the case was approved by the Ethics committee of Istanbul Medipol University. Informed consent to participate was obtained from the patient.

Consent for publication
Informed consent for the publication of clinical data, including laboratory and radiology findings, was obtained from the patient.

Clinical trial
Not applicable.

Competing interests
The authors declare no competing interests.

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