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Hypercalcemia preceding *Pneumocystis jirovecii* infection in a young male post renal transplant

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Abstract
Background: *Pneumocystis* has lung tropism and can cause opportunistic pneumonia. The overall incidence of *Pneumocystis jirovecii* pneumonia (PCP) in solid organ transplantation is 5 to 15% and mortality rates are 13-38%. A timely diagnosis of PCP is difficult and relies on imaging and detection of organism.
Method: We present a case of patients displaying hypercalcaemia with an eventual diagnosis of PCP and treated with a multidisciplinary team approach. We discuss the underlying pathophysiology of hypercalcaemia preceding a diagnosis of PCP. we also reviewed the evidence concerning PJP diagnosis and treatment.
Results: A 34 yrs. old, post Robotic Assisted Renal transplant surgery presented with hypercalcaemia followed by an eventual diagnosis of PCP. We measured their corrected calcium, parathyroid hormone (PTH), 1,25-dihydroxycholecalciferol [1,25-$(OH)_2D_3$] and 25-hydroxycholecalciferol [25(OH)D] levels at admission and following treatment of PCP. The patient diagnosed with PCP after post-transplantation. The patient demonstrated PTH-independent hypercalcaemia (corrected calcium >11.1 mg/dl). The presence of high $1,25(OH)_2D_3$ and low 25(OH)D levels suggest negation of the negative feedback mechanism possibly due to an extrarenal source; in this case, the alveolar macrophages. The patient resolution of their hypercalcaemia after treatment of PCP.
Conclusions: Hypercalcaemia of an unclear aetiology and refractory to treatment in a renal transplant recipient can be a feature of impending PCP In such cases, diagnosis is made of with Radio imaging (CT) assisted by early bronchoscopy may help in speedy recovery and significantly decreasing morbidity and mortality.

Keywords: Hypercalcaemia, immunosuppression, kidney transplantation, *Pneumocystis jirovecii*, transplant, trimethoprim-sulphamethoxazole

Introduction
Pneumocystis jirovecii is a human-specific ascomycetous fungal organism discovered in the 1900s. *Pneumocystis* infection is thought to involve aerosolized particle transmission [1]. *Pneumocystis* colonization may not manifest clinically in immu-nocompetent humans, yet in an immunocompromised patient, *Pneumocystis* has lung tropism and can cause opportunistic pneumonia [1, 2]. The overall incidence of *Pneumocystis jirovecii* pneumonia (PCP) in solid organ transplantation is 5 to 15% [3].
In renal transplant recipients (RTRs), the incidence of P. jirovecii pneumonia (PCP) is 5-15% in patients without prophylaxis, with a greater relative risk up to 6 months post-transplant [3, 4]. Mortality rates are 13-38% in this population [5]. Cytomegalovirus (CMV) infection, glucocorticoid use and recurrent rejection are independent risk factors for PJP [6, 7]. Trimethoprim-sulphamethoxazole (TMP-SMX) prophylaxis [8] is recommended for 3-6 months post-transplant [9-11], which is when most infections occur [3, 10]. Beyond the first-year post-transplant, risk factors for PJP include increased levels of immunosuppression [12], allograft rejection and abnormal renal function [13].
The onset of symptoms is generally fulminant with fever, cough, dyspnoea, and hypoxia. However, PCP may develop some years after transplantation following increased immunosuppression, with less specific symptoms such as sweating, weight loss, cachexia more indolent course.
A timely diagnosis of PCP is difficult and relies on imaging and detection of organism [14].

Case report

A 34 years old male, post renal allograft recipient who came with graft dysfunction and fever, dyspnoea and loose stool; On examination bilateral crepts present, was found to have hypercalcemia and eventual diagnosis of *Pneumocystis jirovecii* Pneumonia was made.

Summary

A 34 yrs. old, post Robotic Assisted Renal transplant surgery in 11th April 2016 with stable baseline sr. creatinine of 1.8 to 2.2 mg/dl presented with fever, dyspnoea, decreased appetite and fatiguability along with loose stool and increased in creatinine to 3.4 mg/dl. On evaluation, he was found to have hypercalcemia (corrected calcium-11.1 mg/dl) and i-PTH-2.3. He was treated with intra venus hydration. His Serum CMV and BK PCR came negative, X-ray chest and USG graft Doppler was normal. After initial improvement, his creatinine started increasing (3.4→2.9->5). His graft biopsy revealed ATN with evolving ACR. His HRCT chest revealed mosaic attenuation? fluid overload and BCM analysis showed overhydration of 2.6 L. patient was afebrile and inj. Methylprednisolone 4 doses-250 mg each were given. He responded, and creatinine decreased to 3.2 mg/dl. He was discharged but had to be readmitted within a week with increasing creatinine (3.2 to 4.2, mg/dl) and hypercalcemia (corrected calcium 13.6 mg/dl). His repeat graft biopsy was s/o recovering ATN. His serum calcium level remained at upper level despite adequate antihypercalcemic measures.1,25$(OH)_2$ VIT D were 187 (47.6-190.32 pmol/l). and repeat i-PTH, was 5.8. His serum ACE levels were normal. X- ray chest showed Rt, midzone opacity, Hence repeat HRCT was done which showed resolution of previous findings, but new atelectasis and consolidation in right middle lobe (not present in previous scan). BRONCHOSCOPY was done and alveolar lavage came positive for *Pneumocystis* Jiroveci and Klebsiella. *Pneumocystis* jiroveci was confirmed on silver methamine staining. Patients received clindamycin and primaquine and other supporting drugs.

He responded to treatment. After 3 weeks of treatment his serum i-PTH increased to 102.6 and calcium normalised. His HRCT shows complete resolution of lesions.

Table 1: Investigations

	1st admission (15th Oct - 27th Oct 2017)		2nd admission (01th Nov - 10th Nov 2017)	
	On discharge	**On admission**	**On discharge**	**On admission**
Haemoglobin	12.1	12.0	11.7	11.0
Total Leukocyte Count	3900	10,100	11,700	6,300
Sr. Albumin	3.1	3.1	3.2	3.9
Sr. Calcium	10.1->11.9	10.1	12.8	9.5
Sr. Phosphorus	5.7		5.5	
Sr. I-PTH	2.3		5.6	102.6
25 OH VIT D	45.1			
1,25 OH VIT D			187 (47.76-190 pmol/L)	
Sr, creatinine	3.4→5 mg/dl	3.2 mg/dl	4.4→ 4.8 mg/dl	3.7 mg/dl
X-ray Chest	Right mid zone opacity			
HRCT THORAX	Bilateral mosaic attenuation (Ground glass opacity)? Fluid overload			

X-ray Chest

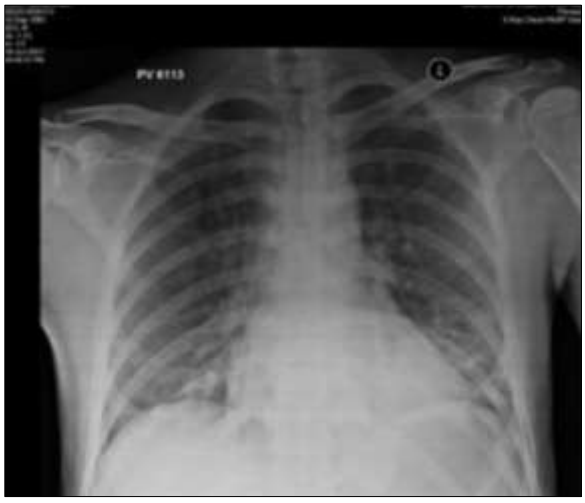

Fig 1: Before admission

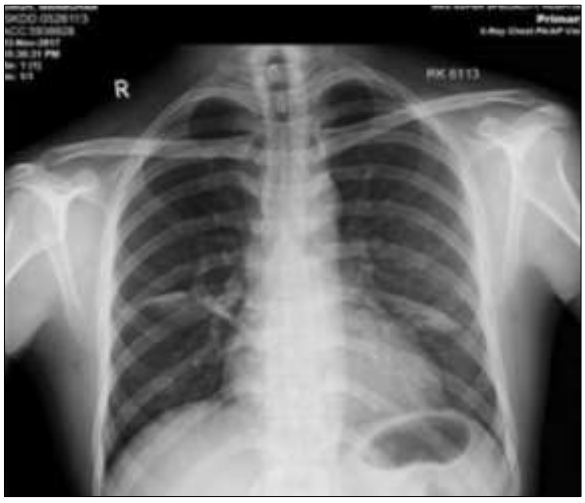

Fig 2: Before discharge

HRCT Thorax

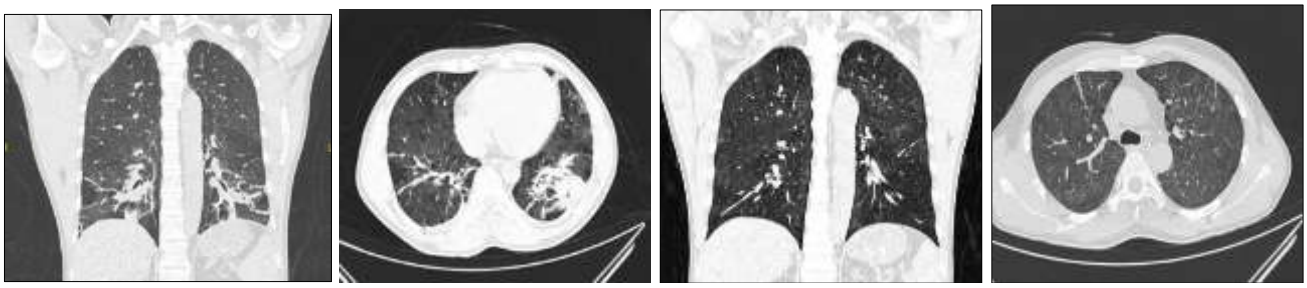

Fig 3: HRCT Thorax

Conclusions

Hypercalcaemia of an unclear aetiology and refractory to treatment in a renal transplant recipient can be a feature of impending PCP. Hypercalcemia may be as preceding manifestation in *Pneumocystis jirovecii* infection. Atypical causes of hypercalcemia should be considered specially in patients with solid organ transplants and immunocompromised state. In such cases, high index of suspicion should be kept and prompt diagnosis with Radio imaging (CT) assisted by early bronchoscopy may help in speedy recovery and significantly decreasing morbidity and mortality.

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