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Pneumocystis Jirovecii Pneumonia in non-HIV immunosuppressed patients: Acase series

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Objective: Increased usage of immunosuppressive medications and lack of guidance about when to initiate primary Pneumocystis Jirovecii Pneumonia (PCP) prophylaxis has led to a rising incidence of PCP in non-HIV immunosuppressed patients. The objective of this case series is to review clinical challenges in diagnosis and management of these patients.

Patients, methods, and results: This is a retrospective case series of all 6 cases which were seen at Jupiter Hospital from January 2020 to October 2021 (Table 1).

Conclusion: The presence of the above-mentioned predisposing factors should raise the suspicion of PCP. Non-invasive investigations like serum LDH, BDG, PET CT scan/HRCT scan of chest can help in the diagnosis. This can be confirmed by BAL PCR, which is both, more sensitive and specific than immunofluorescence microscopy. Trimethoprim- sulfamethoxazole (TMP- SMX), the standard treatment, cannot be used in some circumstances and alternate treatment may have to be used.

Guidance about prophylaxis, antimicrobial therapy for PCP, and adjuvant steroid therapy in non-HIV patients is unavailable, which is an unmet clinical need.

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First report of *Aspergillus tamarii* producing influenza associated invasive pulmonary Aspergillosis

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Objective: Multiple infections can occur after 2009, pandemic influenza, including fungal and bacterial infections, but data from India are limited. To our knowledge, this is the first reported case of influenza-associated invasive pulmonary aspergillosis (IAPA), caused by *Aspergillus tamarii*, after infection with pandemic (H1N1) 2009 which was preceded by COVID-19, 20 months before.

Methods and Results: A 33-year-old male, known asthmatic, had been hospitalized elsewhere in August 2020 with COVID-19 pneumonia for 50 days and had been on mechanical ventilation for 37 days. He had no residual respiratory symptoms 3 months after recovery from COVID-19. He was admitted to Jupiter Hospital in April 2022 with fever, cough, and dyspnea for 8 days, which developed after a cold bath in a temple. HRCT (chest) showed ground glass opacities (GGOs), crazy paving, nodules, and traction bronchiectasis. Review of previous HRCT showed that only GGOs were present (Fig. 1).

At admission, the nasopharyngeal swab was positive for pandemic (H1N1) 2009 in the filmarray respiratory panel and no other pathogen was detected. He was treated with oseltamivir. Expectorated sputum examination showed a heavy load of thin septate hyphae, with acute angle branching, resembling *Aspergilllus* species (Fig. 2). Serum galactomannan was positive (1.8). Based on these features he was diagnosed as a case of probable IAPA and initiated posaconazole (PCZ) treatment. Sputum fungal culture was positive and was identified by MALDI TOF MS as *A. tamarii*. *A. tamarii* has been rarely encountered as a human pathogen. Case reports of its involvement in eyelid infection, keratitis, invasive sinonasal infection, and onychomycosis exist. Sensititre MICs were 0.0625 mcg/ml, 0.125 mcg/ml, 0.0625 mcg/ml, and 0.125 mcg/mL for itraconazole, voriconazole, PCZ, and for isavuconazole (ISVCZ) respectively.

The usually obtained PCZ trough level with standard dose is 1.2 mg/l which generates AUC of 200R. The usually obtained ISVC) trough level with standard dose is 3 mg/l which generates AUC of 100R. The PKPD index, AUC/MIC of 100, is needed with both these azoles for a therapeutic effectR. Therefore, it would be possible to treat this infection with any of these azoles.

PCZ was continued in view of the easy availability of therapeutic drug monitoring (TDM) to assure adequate drug exposure, lower cost, and clinical improvement which had already occurred.

Conclusion: An infection due to a rare *Aspergillus* species needs correct identification, MIC determination, and PKPD consideration for appropriate drug selection and management.

Table 1

Case no	Etiology	Manifestations and interval between onset of symptom and diagnosis	Radiology	LDH (U/L)	BDG (pg/ml)	PCR (copies/ml)	Treatment	Steroids	Outcome	Secondary prophylaxis
1	RA on Methotrexate, Prednisolone, Rituximab	Fever, dry cough, dyspnoea, desaturation 60 days	HRCT: typical	ND	>523	ND	Caspofungin TMP- SMX	High dose needed Impossible to taper down Attempt led to need for ventilator	Severe oral HSV Secondary VAP Klebsiella pneumoniae, Psuedomonas aeruginosa bacteremia Expired	–
2	RA on Methotrexate, Prednisolone, Leflunomide	Fever, dyspnoea, desaturation 28 days	HRCT: typical	ND	>523	BAL 140052	TMP SMX		Cured	TMP SMX
3	Post renal transplant Past PCP (was not on primary prophylaxis) CMV	Weight loss 7- 8 kgs Fever (more towards evening) Desaturation (5 min walk test +) 56 days	PET CT: typical	281	>523	BAL> 112000	Clindamycin Primaquine Caspofungin TMP SMX was avoided due to possibility of renal decompensation & hyperkalemia	Increased	Cured	TMP SMX
4	ITP steroids, Azathioprine Recent CMV with ongoing treatment	Fever Weight loss 10kg 75 days	HRCT: typical	337	ND	ND	Clindamycin Primaquine Caspofungin TMP SMX avoided due to concurrent vGCV	Increased	Cured CMV recurred	TMP SMX
5	GBM Temozolamide Radiotherapy	Fever, dry cough Desaturation 7 days	HRCT: typical	291	266	ND	Clindamycin Primaquine Caspofungin TMP SMX avoided due to neutropenia	Increased	Neutropenia recovered & IRIS developed worsening sats & imaging abnormalities	TMP SMX
6	RA on Methotrexate, Prednisolone, Leflunomide	Dry cough Desaturation 21 days	HRCT: atypical for PCP	ND	>523	454864	TMP SMX	Increased	Improved (on treatment)	–

Typical findings for PCP in HRCT: Ground glass opacity [GGO] in lung parenchyma with peripheral and basal sparing, vGCV: Valganciclovir, GBM: Glioblastoma multiforme, TMP- SMX: Trimethoprim-sulfamethoxazole

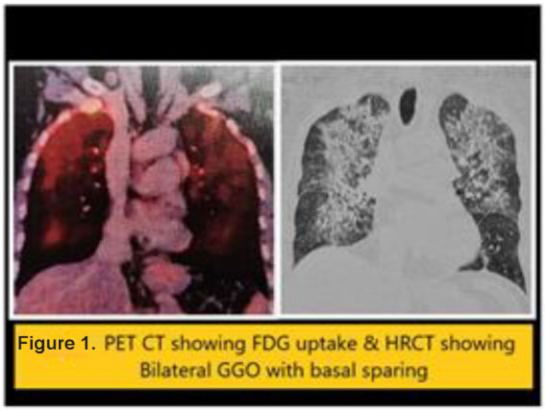
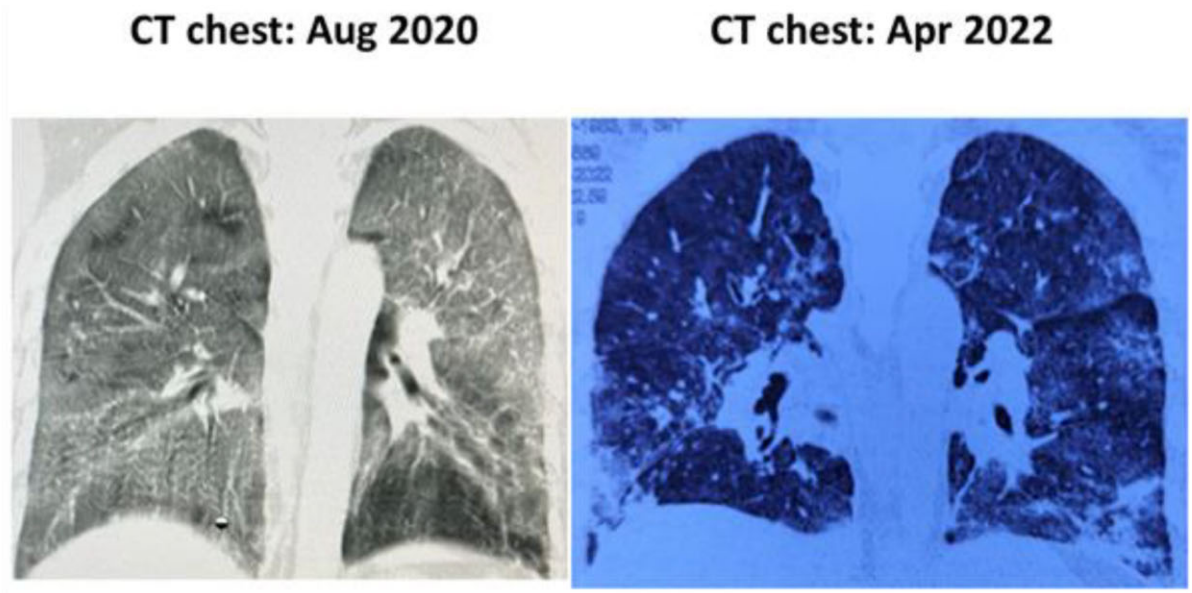


Figure 1. PET CT showing FDG uptake & HRCT showing Bilateral GGO with basal sparing

Figure 2. PET CT showing FDG uptake & HRCT showing Bilateral GGO with peripheral sparing



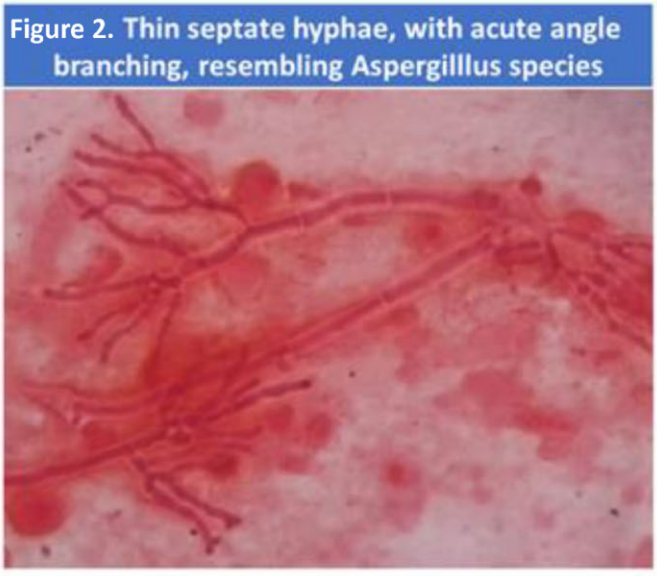


Figure 2. Thin septate hyphae, with acute angle branching, resembling Aspergilllus species


Figure 2. Fungal growth on SDA

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PK PD rationale and efficacy of isavuconazole treatment after failure of amphotericin B and posaconazole for COVID-19 associated cranial Mucormycosis

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Objective: This case series describes our experience of using isavuconazole (ISVCZ), along with TDM, after the failure of treatment with Amphotericin B (AmB) and Posaconazole (PCZ) due to the better PK PD properties of ISVCZ.

Patients and methods: There were 6 patients with ROCM who had disease progression despite surgical debridement and adequate treatment with AmB and PCZ. Anti-fungal treatment was switched to ISVCZ which achieves levels in brain (1.86x)R and in bone-marrow (3x)R as compared to serum levelsR.

Results: PK PD considerations for ISVCZ treatment considering the likely levels in brain and bone-marrow and the MIC of majority of Mucoralean molds as ≤4R

Table 1

Table 2

Results of treatment

Conclusion: Treatment with ISVCZ may mitigate some of the challenges in ROCM due to its PK PD properties. TDM for ISVCZ is not routinely recommended, but could be used to ensure high plasma exposures and enhanced penetration to the site of infection. Our results are encouraging although there are several limitations of a case series, confounding variables involved, and the use of ISVCZ as salvage after failure of previous treatment.

Clinical success in this series suggests that extrapolative PK PD considerations in using ISVCZ for such 'difficult to treat' patients may be justified.