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THE EXCHANGE

Issue 55
October 2022

A Knowledge Sharing Initiative by Medanta

Rare Case of Adverse Cutaneous Drug Reaction

Overlapping Stevens Johnson Syndrome and Toxic Epidermal Necrolysis

Stevens-Johnson Syndrome (SJS) is a rare but serious immune-mediated disease characterised by a prodromal illness followed by severe mucocutaneous symptoms. It is rapid, progressive and episodic in nature involving T-Cell mediated response to keratinocytes. It has high morbidity and mortality, which can be due to hypovolemia, electrolyte imbalance, septic shock and multi-organ failure. It has constitutional symptoms, including fever, malaise, myalgia, rash, arthralgia and anorexia. SJS can either be caused by medications, hypersensitivity reaction or infection. When the severity increases, it is followed by Toxic Epidermal Necrolysis (TEN).

Several drugs are at high-risk of inducing SJS and TEN, including Allopurinol, Trimethoprim-Sulfamethoxazole, Sulfonamide, Aminopenicillins, Quinolones, Anti-Epileptic Drugs and Oxicam-Type Nonsteroidal Anti-Inflammatory Drugs (NSAIDS) . However, infectious aetiologies are also prevalent with the most common ones being mycoplasma pneumonia and enterovirus.

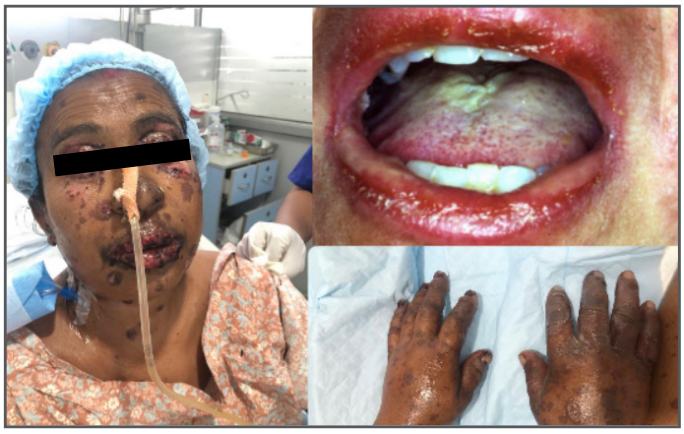
The degree of total body surface area (TBSA) involved determines where on the SJS/TEN spectrum a patient lies (SJS: <10% TBSA; SJS-TEN overlap: 10%-30% TBSA; TEN: >30% TBSA). Currently, SJS and TEN conditions, both, are together known as a single entity called Epidermal Necrolysis (EN).

SJS lesions are generally described as macules with purpuric rashes followed by large vesiculobullous lesions. The large wound areas may cause severe pain, massive fluid and protein loss, electrolyte imbalance, bleeding, evaporative heat loss with subsequent hypothermia, insulin resistance, hypercatabolic state, infection and bacteraemia, hypovolaemic shock with renal failure, and multiple organ dysfunction.

SJS/TEN is a medical emergency that requires urgent hospitalisation with Intensive Care Unit (ICU) admission. Treatment focuses on removing the cause, caring for wounds, controlling pain and minimising complications. The intensivist plays a critical role in the treatment of SJS/TEN and this is reflected in early detection, withdrawal of offending agents, initiating resuscitation, managing complications and providing supportive care.

Case Study

A 60-year-old female patient with no previous comorbidity came to the Emergency Department of Medanta-Ranchi with complaints of rashes over face, ear, neck and extremities with ulcerations of mouth, axilla and perineal areas since 4 days.



Patient at the time of admision showing atypical purpuric and bullous target lesions on face, neck and lips. There was haemorraghic crusting of the lips, mucopurulent discharge from her eyes and skin rash with bullae formation

The patient had developed fever and redness of eyes for which she took Ciplox eye drops and tablet Nimesulide from a local medicine shop. Initially, on Day 3, she had a rash that was non-pruritic and painless involving her neck, chest, back, abdomen, thighs, legs, palms

and soles. Within 24 hours, these lesions progressed to widespread bullous, erythematous pruritic lesions involving the eyelids, hemorrhagic crusts over lips ulceration and bleb formation over the palms. Oral and genital mucosa was simultaneously affected.
Around 20% of the body surface area involved skin detachment. On examination, she looked toxic and febrile with 102°F body temperature. Her blood pressure was 80/50 mmHg, and she was tachypneic (RR-30/ min) with tachycardic (HR-120/ min), maintaining SpO2 of 96% on 8 L/min of oxygen. She was shifted to the Critical Care Unit (CCU) for further management. There she was evaluated clinically with point-of-care ultrasound (POCUS) followed by fluid resuscitation, antimicrobial therapy and supportive care as per surviving sepsis guidelines. On further examination, her oral lesions revealed haemorrhagic crusted lips with difficulty in mouth opening. Ocular examination showed bilateral congested conjunctiva with matted eyelashes having mucopurulent discharge. Genital examination revealed multiple erosions over her vulva with difficulty in urination. Nikolsky sign was positive, but other systemic examinations were normal. On the basis of history and clinical examination, she was diagnosed with SJS-TEN Overlap Syndrome. She did not have a history of any previous drug allergy.

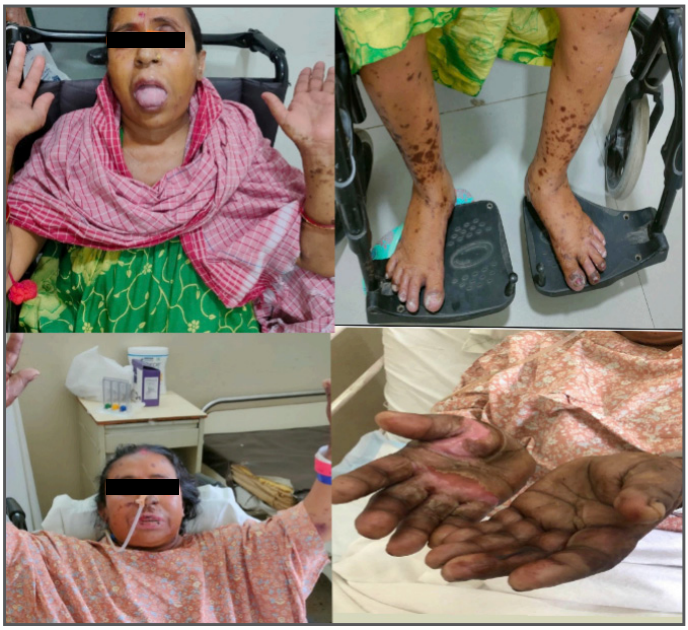
- Her complete blood count (CBC) showed haemoglobin (Hb)-9.4 gm/dl, total leukocyte count (TLC)-30,400/ mm3, platelet count-280,000/mm3, erythrocyte sedimentation rate (ESR)-52mm/h. Liver function test (LFT) showed serum glutamic oxaloacetic transaminase (SGOT)-295 IU/L, serum glutamic-pyruvic transaminase (SGPT)-462 IU/L, random blood sugar (RBS) was 262 mg/dl. Chest X-ray revealed bilateral pneumonic patches whereas the coagulation profile, renal function test, bilirubin, serum electrolytes, anti-nuclear antibody (ANA) were within normal limits.
- Blood, urine and wound swab culture were negative.
- Serological studies for Herpes, Epstein Barr Virus (EBV), and Cytomegalovirus (CMV) were negative.

Due to the high risk of mortality, she was evaluated for the prognosis using Severity-of-illness Score for Toxic Epidermal Necrolysis (SCORTEN) index which came as 4 with a predicted mortality of 58.3%. She was managed with a multidisciplinary approach in CCU with strict barrier precaution. She was started with injection Methylprednisolone 1gm for 3 days in conjunction with supportive therapy - antibiotic eye drops, oral care, vaginal hygiene, adequate hydration and nutritional support. Injection Meropenem and Clindamycin were started as part of antibiotic regimen and to prevent super-added infections during the course of disease.

Severity-of-illness Score for Toxic Epidermal Necrolysis (SCORTEN)

Prognostic factors	Points
Age > 40 years	1
Tachycardia > 120bpm	1
Neoplasia	1
Initial Detachment > 10%	1
Serum Urea > 10mmol/L	1
Serum Bicarbonate < 20mmol/L	1
Blood Glucose > 14mmol/L	1

SCORTEN	Mortality (%)
0-1	3
2	12
3	35
4	58
>= 5	90



Patient showing hyper-pigmentation during recovery phase

Ophthalmology, gynaecology and dermatology consultations were also taken and treatment was modified accordingly. Her lesions improved gradually

after Intravenus (IV) steroid administration. She was on parenteral steroids for 1 week and then oral steroids for 1 more week with tapering dosage. She improved gradually and was discharged on Day 15 of hospitalisation. Regular follow-ups showed gross improvement in previous lesions.

Discussion

The incidence of SJS is estimated to be between 1.1 and 7.1 cases per million persons per year. As per our observation, this was a case of drug-induced SJS-TEN Overlap Syndrome. SJS is classified as secondary to drugs when the patient has a history of taking the offending drug within 8 weeks of the onset of symptoms. In India, Nimesulide is easily available as an over the counter (OTC) drug. SJS/TEN occurs most commonly as an idiosyncratic reaction to systemic medications. In this case, the diagnosis of drug-induced SJS-TEN was based on patient history, clinical examination and laboratory findings. To evaluate prognosis in this case, we used SCORTEN disease severity index to predict the mortality of >58.3%. Early intervention has a significant effect on morbidity and mortality. Withdrawal of the offending drug has been shown to decrease mortality and improve prognosis. SJS/TEN is a devastating and potentially fatal mucocutaneous disease. Early diagnosis, immediate referral to an Intensive Care Unit for resuscitation, definitive management, supportive care and multidisciplinary efforts form the pillars of treatment. Surviving patients and their families should be educated to avoid offending medications and their analogs.

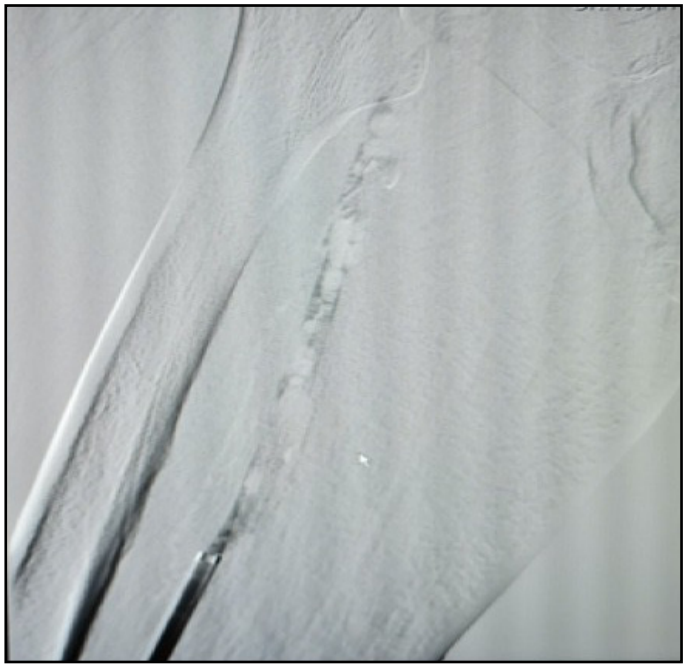
Dr. Tapas Kumar Sahoo
Associate Director and Head
Institute of Critical Care
Medanta - Ranchi

Medanta@Work

Endovascular Aspiration Thrombectomy

Saving a Transplanted Kidney

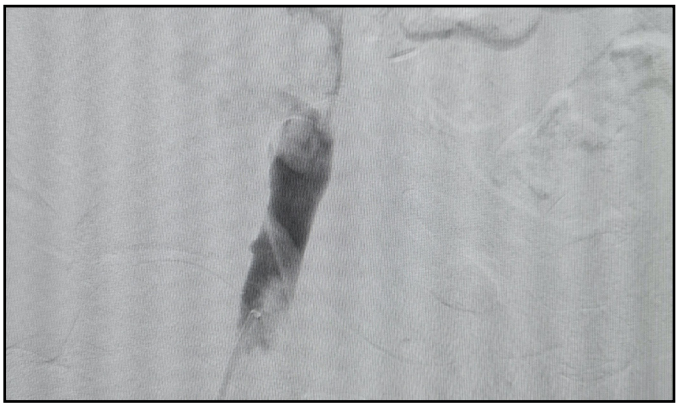
A 47-year-old man had undergone a living-donor kidney transplantation in the right iliac fossa at another hospital 3 months prior to being presented to the Emergency Department of Medanta-Lucknow with symptoms of anuria and right lower limb swelling for 10 hours. An emergency Doppler ultrasound revealed right lower limb deep vein thrombosis (DVT) extending to the right external iliac vein.



Venogram showing thrombus within common femoral vein

A Doppler ultrasound of the graft renal vein showed no obvious colour flow with reversal of diastolic flow in the graft renal artery. Thus, diagnosis of acute kidney injury (AKI) secondary to transplant renal vein thrombosis and external iliac vein thrombosis was established. Patient's serum creatinine value was 2.68 with mild enlargement of the graft kidney suggestive of oedema within the graft parenchyma. Further, CT pulmonary angiogram was performed to look for any pulmonary vein embolism and screening was done to understand the extent of DVT.

CT showed thrombus involving the right common femora vein, external iliac vein, graft renal vein and common iliac vein. After extensive discussion of risks and benefits by the multidisciplinary team, in view of salvageability of graft kidney due to long duration of renal vein thrombosis, the patient's consent was taken and he was taken up for therapeutic endovascular intervention.

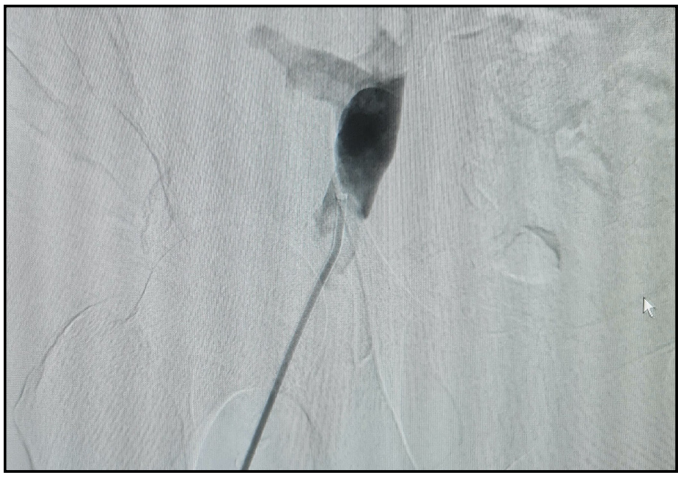


Pre-mechanical thrombectomy showing thrombus in graft renal vein (arrow)

To prevent migration of clots during thrombectomy, an infra renal inferior vena cava (IVC) filter was deployed.

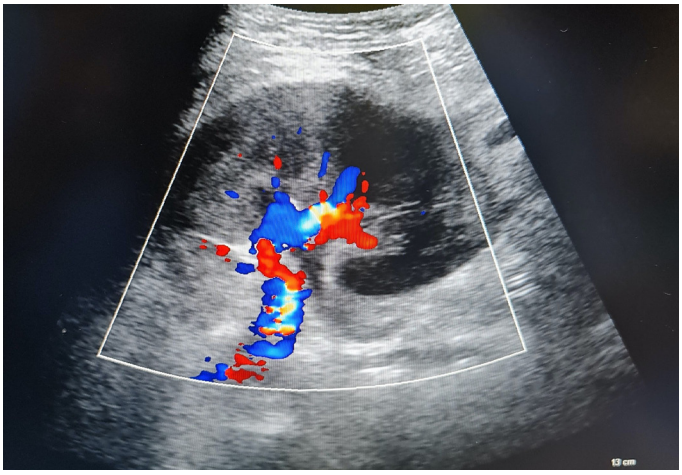
Popliteal vein access was taken and aspiration thrombectomy was done from common femoral vein to common iliac vein along with gentle aspiration for the graft renal vein keeping in mind the history of recent anastomosis.

There was significant clearance of the thrombus after multiple passes of aspiration to clear all the clots from the right external iliac vein and graft renal vein.



Post-mechanical thrombectomy showing graft renal vein free of thrombus

Venogram performed at the end of the procedure showed good flow in the transplant renal vein. After the thrombectomy transplant, Doppler ultrasound showed good arterial and venous waveform.



Doppler ultrasound of graft renal vein showing complete recanalization of renal vein post mechanical thrombectomy

Urgent dialysis was done immediately after the procedure and the patient was then started on intravenous (IV) unfractionated heparin for 3 days to maintain activated partial thromboplastin time (APTT) of 80 to 100. Gradually, his urine output increased over the next 3 days and the elevated creatinine values started coming down. Patient had serum creatinine level of 0.69 at the time of discharge with total recanalisation of graft renal vein and near total recanalisation of iliac vein.

In several case series in literature, it has been observed that iliofemoral DVTs appear to affect renal allograft function despite sparing the allograft vein. Anticoagulation is a reasonable initial approach if the allograft vein is not involved. However, if anticoagulation fails, or if the allograft vein is involved, then immediate endovascular intervention in the form of thrombectomy, angioplasty, or stenting can be a graft salvaging technique for organ transplant patients.

Dr. Raj Kumar Sharma
Director - Nephrology and Kidney Transplant Medicine
Kidney and Urology Institute
Medanta - Lucknow

Dr. Rohit Agarwal
Senior Consultant
Radiology and Imaging
Medanta - Lucknow

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In Focus

A Rare Case of Cystic Lung Disease in a Male Patient

Lymphangioleiomyomatosis (LAM) is characterised by the proliferation of abnormal smooth muscle cells (LAM cells) in the lungs, lymph nodes, or other organs. LAM is more common in woman and many a times associated with chylothorax.

Case Study

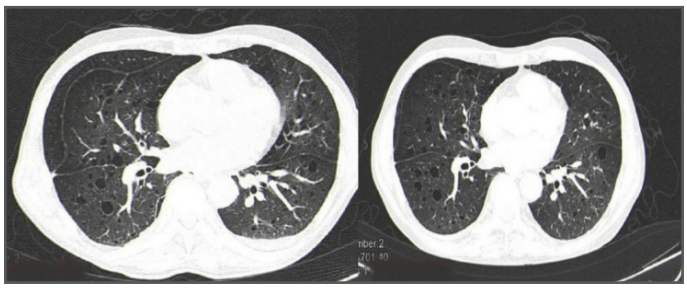
A 59-year-old man presented to Medanta-Gurugram with dry cough, breathlessness, chest pain, weight loss, weakness and right-sided pleural effusion. He was put on anti-tubercular treatment (ATT) by the referring hospital. A lifelong non-smoker with a history of pulmonary tuberculosis (TB) treated with a course of ATT 40 years ago, the patient had lost his hearing permanently to an early childhood trauma.

Milky white pleural fluid

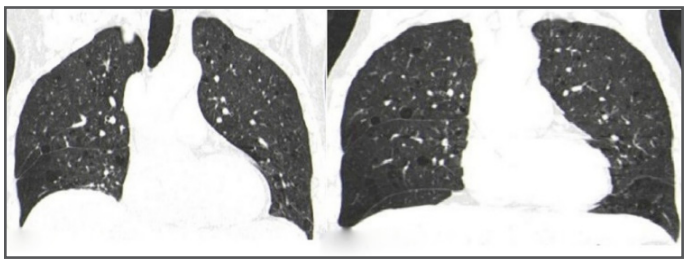
ICD bag with chylous effusion

His initial blood reports were inconclusive, except chest X-ray, which showed right-sided pleural effusion. Whitish fluid was obtained on diagnostic tapping and was subsequently cleared using an intercostal drainage (ICD) tube inserted on the right side. A pleural fluid analysis revealed total protein 2.4gm/dl, glucose 121mg/dl, total leucocyte count 682 cells/microlitre, adenosine deaminase (ADA) 12.27U/L and triglycerides 153mg/dl. The TB GeneXpert test was negative, so a diagnosis of chylothorax was established.

A high-resolution computed tomography (HRCT) of the chest revealed diffuse emphysematous changes with multiple cysts throughout both the lungs. A diagnosis of cystic lung disease was made with differential diagnosis of LAM, Langerhans cell histiocytosis (LCH) and pneumocystis jirovecii pneumonia (PCP).



Axial view chest CT images done on 9.10.2021 and 30.1.2022 respectively, showing uniform distribution of multiple thin walled well defined cysts with slight visible improvement



Coronal section chest CT images done on 9.10.2021 and 30.1.2022 respectively, revealing diffuse emphysematous changes with multiple cysts throughout both the lungs with slight visible improvement

For further evaluation of cystic lung disease, bronchoscopy-guided transbronchial lung biopsy (TBLBx) was done. Tru-cut biopsy and histochemical stains showed thin-walled cystic air spaces and patchy disordered, clustered to nodular proliferation of bland spindled and cuboidal epithelioid cells around airways, lymphatics and blood vessels.

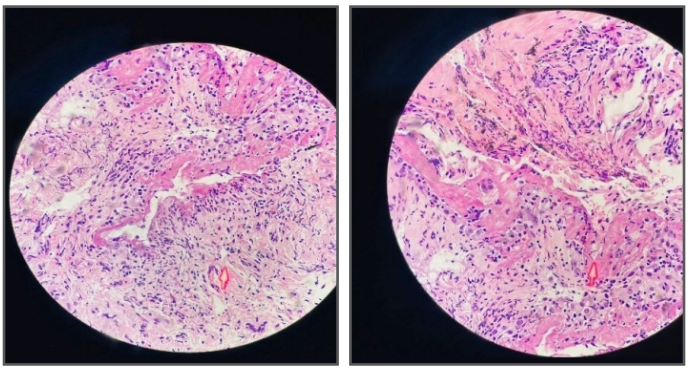
The diagnosis of LAM/cystic lung disease with chylothorax - a very rare entity in a male patient - was confirmed after he tested positive for immunohistochemistry markers vimentin, smooth muscle actin (SMA) and human melanoma black (HMB45).

The patient was started on oral Sirolimus 2mg once a day and medicines for treatment of other symptoms. Patient showed significant improvement in terms of clinical and physiological parameters.

After 3 months, the follow-up chest HRCT showed that the disease has stabilised. The spirometry values, including forced expiratory volume (FEV1) and forced vital capacity (FVC), which were 1.06 litres and 1.72 litres pre-treatment, had improved to 1.51 litres and 2.51, respectively (42% improvement in FEV1 and 46% in FVC from baseline).

Discussion

LAM is a rare lung disease traditionally affecting women during their childbearing age. It could be sporadic i.e. associated with tuberous sclerosis syndrome (TSC). It manifests in the lungs, kidneys, and the lymphatic system.



High power microscopy images showing thin-walled cystic air spaces with disordered, clustered to nodular proliferation of bland spindled and cuboidal epithelioid cells, around airways, lymphatics, blood vessels

Sporadic LAM (TSC LAM) approximately affects 1 in 4,00,000 adult women. The association of LAM with TSC in women is as high as 30%-40%. LAM is extremely rare in men, but has been reported along with TSC. In this case, the disease was detected in a 59-year-old patient. The characteristics of LAM are poorly explained; they may exist with or without pleural effusion.

In the present case, pleural effusion was transudative chylothorax (fluid triglyceride-153mg/dl). Though LAM is a cystic lung disease, it can present with either of the pleural pathology - pneumothorax or chylothorax. A study found that 55% patients with sporadic or TSC LAM have pneumothorax and 21%-28% have pleural effusion during the course of the disease. Rupture of any cyst can lead to pneumothorax. Mechanisms that could be associated with chylothorax in LAM include:

- Chyle leaking from the thoracic duct or its tributary branches due to proximal lymphatic obstruction or direct involvement
- Oozing of chyle from pleural lymphatic/collateral vessels, and
- Transdiaphragmatic flow occurring through chylous ascites.

Immunohistochemistry for SMA/desmin and HMB45 are an important adjunct to diagnosis. HMB45 is particularly useful in samples obtained through transbronchial biopsy. In our patient, transbronchial lung biopsy was done where the sample was positive for vimentin, SMA and HMB45, which is confirmatory for LAM.

Patients with chylothorax can be managed conservatively. This includes nil per oral (NPO)/enteral diet, total parenteral nutrition, draining of pleural space with ICD tube for complete lung expansion. Drainage of chylous fluid is measured on daily basis. The conservative management is done for 1-2 weeks. Our patient was treated on similar lines. Total 950ml-1,000ml fluid was drained and the tube was removed after 5 days. Sirolimus stabilises lung function, decreases serum vascular endothelial growth factor-D (VEGF-D) levels, reduces symptoms and helps improve quality of life.

Sirolimus (also known as Rapamycin) stops mTOR activation of downstream kinases and restores homeostasis in cells in the company of defective TSC gene function. Our patient responded very well to Sirolimus treatment and showed gradual improvement that was seen during the 3-month follow-up.

Though LAM is uncommon in men, it is recommended to always do lung biopsy and immunohistochemistry testing for confirmation of diagnosis.

Dr. Ashish Kumar Prakash
Senior Consultant
Respiratory and Sleep Medicine
Medanta - Gurugram

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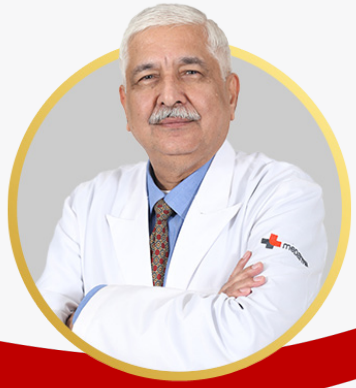
Kudos

Dr Rakesh Kapoor Gets Award of Excellence



Medical Director &
Director - Urology & Kidney Transplant Surgery
Medanta - Lucknow

Medanta congratulates Dr. Rakesh Kapoor on getting an Award of Excellence for his contribution to the fields of Endourology, Reconstructive Urology and Excellence in Teaching. The award was given in the presence of the President of the Republic of Mauritius Prithvirajsing Roopun at the second edition of the Indo-Mauritius Urology Conclave. The event was aimed at providing a common platform for accomplished medical professionals to share their knowledge and experience to enhance urological services, including kidney transplant.

Welcome Onboard

Dr. Anshul Gupta

Director - Haemato-oncology and Bone Marrow Transplant
Medanta - Lucknow

Haematologist and Bone Marrow Transplant physician with expertise in treating various blood-related disorders, lymphomas, multiple myeloma, myelodysplastic syndrome in addition to genetic disorders such as thalassemia, sickle cell anemia and haemophilia.

Dr. Sandeep Kumar Verma

Associate Director - GI Surgery, GI Oncology and Bariatric Surgery
Medanta - Lucknow

Gastrointesinal surgeon with expertise in laparoscopic and open management of GI cancers, pancreatic and anorectal surgeries.

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Dr. Neelam Bisht

Senior Consultant - Internal Medicine
Medanta Mediclinic - Delhi

Physician with expertise in diagnosis and management of infections across various specialities.

Dr. Nilesh Mishra

Consultant - Institute of Musculoskeletal Disorders and Orthopaedics
Medanta - Ranchi

Orthopaedician with expertise in performing arthroscopic and trauma surgery.

Dr. Vijaya Mohan

Senior Consultant - Paediatrics
Medanta - Lucknow

Paediatrician with expertise in managing all types of illnesses in children of 0-19 years and a certified adolescent health specialist.

Dr. Rajesh Kumar Jaiswal

Consultant - Nephrology
Medanta - Lucknow

Nephrologist with expertise in managing complex kidney diseases, haemodialysis and peritoneal dialysis, interventional nephrology in addition to kidney transplantation.

For **EMERGENCY** DIAL **1068**

Medanta - Gurugram
Sector - 38, Gurugram, Haryana | Tel: 0124 4141 414 | info@medanta.org

Medanta - Lucknow
Sector - A, Pocket - 1, Sushant Golf City,
Amar Shaheed Path, Lucknow I Tel: 0522 4505 050

Medanta - Indore
Plot No. 8, PU4, Scheme No. 54, Vijaynagar Square,
AB Road, Indore I Tel: 0731 4747 000

Medanta - Patna
Jay Prabha Medanta Super-Specialty Hospital, Kankarbagh Main Road, Kankarbagh Colony, Patna I Tel: 0612 350 5050

Mediclinic - Delhi
E - 18, Defence Colony, New Delhi
Tel: 011 4411 4411

Medanta - Ranchi
P.O. Irba, P.S. Ormanjhi, Ranchi I Tel: 1800 891 3100

Mediclinic Cybercity - Gurugram
UG 15/16, DLF Building 10 C, , DLF Cyber City,
Phase II, Gurugram I Tel: 0124 4141 472

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