Volume 1, Issue 1 Oct 23

GOKULAM Academic Pulse

Breaking Barriers:
Bridging the Academic GAP.

Official Publication of Sree Gokulam Medical College & Research Foundation

Vice chairman's message

Gokulam Academic Pulse, is a unique initiative that brings up clinically and therapeutically challenging disease entities before the inquisitive clinicians among the faculty and residents. It is appropriate that the head of the institution Dr. Lalitha Kailas (Principal) herself has reported the first case in the first issue, a case of diagnostic dilemma between ITB (Intestinal Tuberculosis) and IBD (Inflammatory Bowel Disease) in a 10-year-old boy presenting with recurrent fever, abdominal pain and growth retardation. While the leader of the editorial team, Dr. Nirmal George (Associate Professor, Pharmacology) presents an explanatory article on drug use in kidney disease, equally interesting cases are seen to be reported from the departments of Microbiology, Surgical Oncology, Dermatology and Interventional Radiology. After going through the presentations let me congratulate all the authors who contributed case reports in a systematic way enabling the editorial board to publish a knowledge worthy academic handout for reading. It is appropriate to congratulate the members of the editorial team, Dr. S Bhasi, Dr. Vivek George, Dr. Krishna, Dr Geetha O, Dr. Keba J for their valuable efforts towards making this e-magazine a reality.

Wishing a great future for the venture.

Dr K K Manojan

Vice chairman

SGMC & RF

Dean's message

I am extremely delighted to understand that our Academic Magazine, Gokulam Academic Pulse Volume 1 Issue 1 is ready for the official launch. Let me congratulate Dr Lalitha Kailas the Principal for her unwavering efforts in converting the magazine into reality. I would also like to congratulate Dr Nirmal George, Dr S Bhasi, Dr Krishna, Dr Vivek George, Dr Geetha O, Dr Nirmal George and Dr Keba J, 'the editorial team' for their valuable and consorted efforts in having compiled all clinically and academically interesting case reports from various departments. I should also congratulate the authors of the articles, who made this magazine possible. The content of the magazine is again quite exciting with genuine diagnostic and treatment dilemmas. The principal has led us by example by being the author of the first article and the editorial team has also done an informatory article on pharmacological considerations of drug use in Chronic Kidney Disease. The case reports from departments of Dermatology, Surgical Oncology and Interventional Radiology are also quite interesting.

Let me wish the very best for this Magazine to get metamorphosed into a standard magazine from Sree Gokulam Medical College.

Dr. Chandramohan P

Dean Emeritus

SGMC & RF

Foreword

I am proud and delighted to inscribe the foreword for the first volume of our institutional e – Magazine "**GOKULAM ACADEMIC PULSE** ". This is a humble attempt to compile scientific sessions presented in the monthly academic meet of our institution. Gokulam Academic Meet, started around 3 years back with the purpose of giving opportunity for various departments to showcase their expertise and services in their concerned speciality.

The topics presented by the faculty and residents are interesting or difficult to diagnose cases. These are translated into a readable format in this ***Gokulam Academic Pulse***. I am extremely thankful to Dr. Nirmal George (Associate Professor, Pharmacology) for the enthusiastic initiative taken as the leader of the editorial team for designing this in a unique manner. I also acknowledge the other members of the editorial board Dr. S. Bhasi (Professor Emeritus, General Medicine), Dr. Krishna. G (Professor, Pathology), Dr. Vivek George (Professor and Head, Pathology), Dr. Keba J (Associate Professor, Physiology), Dr. Geetha. O (Professor and Head, Forensic Medicine) for their enthusiastic co-ordinated efforts.

All the articles or case scenarios have been thoroughly revised and updated in a novel readable style and have undergone multiple reviews by our editorial team. This multi authored magazine has been made possible because of the contributions from the faculties and residents of various departments, who have willingly shared their experience and expertise and taken time to write for this e-magazine "Gokulam Academic Pulse" I am deeply indebted to all of them.

This novel venture is the culmination of efforts of many people and comes with a promise - the perfect is yet to come.

Dr. Lalitha Kailas

PRINCIPAL

SGMCRF

Editorial

Academic activities among the teachers are one among the trade secrets of a successful Institution of excellence. Sree Gokulam Medical College & Research Foundation has a long heritage of '**Monthly Academic Meet**' among faculty and residents. The meet is an interdisciplinary platform where relevant topics, interesting cases, findings and case series are presented. '**Gokulam Academic Pulse (GAP)**' is our humble attempt at transcribing these academic activities into readable format.

The purpose of 'Gokulam Academic Pulse' is to discourse the relevant scientific observations from the institution to the scientific community. The articles are presented as interesting scenarios and depictions so as to kindle curiosity in the reader's mind. This might reflect to higher rates of reading and retention compared to academic books.

The first volume of GAP comprises of articles from the specialties, Paediatrics, Microbiology, Pharmacology, Dermatology, Oncology and Radiology. Kindly enjoy the read!

Editorial committee

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Intestinal tuberculosis or Crohn's disease – A classic "Whodunnit" Tale

Authors

- Dr Lalitha Kailas & Dr Fibi CS

Correspondence

- Dr Keba J

Synopsis (Read at your own risk – May contain Spoilers!)

A 10-year-old boy with recurrent fever, abdominal pain and growth failure was evaluated and the cause was narrowed down to either intestinal tuberculosis (ITB) or inflammatory bowel disease (IBD). This narration follows the investigators' journey to ultimately finding out who the culprit really was among the two. This case is being reported to highlight the difficulty in differentiating Crohn's disease from intestinal tuberculosis.

Prologue

- There is an increase in the incidence of paediatric-onset IBD & Gastrointestinal tuberculosis in India.
- Distinguishing tuberculosis (TB) and Crohn's disease in patients with vague complaints is a huge diagnostic challenge as both have overlapping features and treatment also varies for both.
- What follows next is a report of one such challenge, dealt successfully by the authors.

Act 1 – The Patient and his history

A 10-year-old boy was brought to the hospital with history of recurrent episodes of fever for the past 7 months, vomiting, abdominal pain, loss of appetite and loss of weight for 4 months. Parents also noticed that the child was not growing well (not gaining weight or height appropriate for age) from the age of 5-6 years.

Negative history - No history of (h/o) contact with TB or h/o any significant illness like recurrent respiratory infections or chronic diarrhea or bloody stools, no history of chronic gastrointestinal illness in the family.

Prior investigations

- Serial decreases in Hemoglobin
- ↑ in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and platelet count.
- USG abdomen - para-aortic & iliac lymph nodes.
- Brucella IgM & IgG, EBV IgM and ANA - negative.

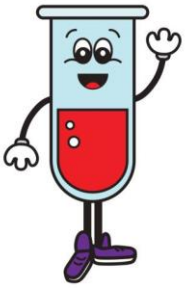
Act 2 – The Physical Examination

Appearance – A grossly emaciated child.

Parameter	Actual	Expected
Weight (Kg)	16	30
Height (cms)	120	137

- BMI-11 kg/m^2 (3 standard deviations below normal)
- **General Examination** – Pallor +. No other significant findings.
- **CVS, RS, CNS examination** – No gross abnormalities noted.
- **GIT examination** - Abdomen was soft, non-distended with tenderness in right iliac fossa. No ascites, hepatosplenomegaly, aphthous ulcers or anal fistula.

Act 3 – The preliminary investigation



- Hemoglobin – 9g/dl (↓)
- CRP – 77 (↑)
- ESR – 102mm/hour (↑)
- Platelet count – 4.5lacs/cu.mm (↑)
- Serum Albumin – 2.3g% (↓)

Act 4 – The two suspects

- History of prolonged fever, vague abdominal complaints, and laboratory evidence of elevated acute phase reactants and hypoalbuminemia, points to either **intestinal TB or pediatric IBD-Crohn's disease**.
- Irregular fever, vague abdominal symptoms, anemia, thrombocytosis, hypoalbuminemia with increased ESR and CRP values are seen in both IBD and intestinal TB.
- Scientific literature suggests impairment of growth parameters can precede the intestinal mucosal lesions by months to years in pediatric CD. Considering this growth failure of longer duration, the possibility of CD could not be ruled out.

Act 5 – The dilemma

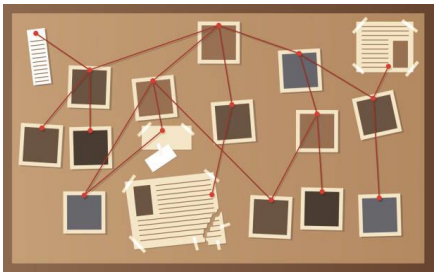
The ultimate course of these two disorders is very different.

- TB is an entirely **curable** disease.
- CD is a **progressive and relapsing** illness and requires lifelong treatment and follow up.
- Misdiagnosis and inappropriate treatment of ITB as CD with immunosuppressive medications can lead to worsening of ITB.
- CD may show some response to antitubercular treatment (ATT) which may delay the correct diagnosis of CD and thereby put patients at risk of exacerbation and complications.

Hence correct diagnosis at the earliest stage is critical.

Act 6 – The search for truth

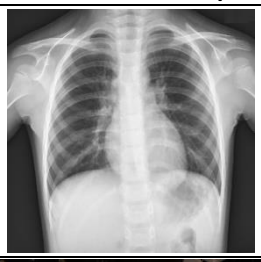
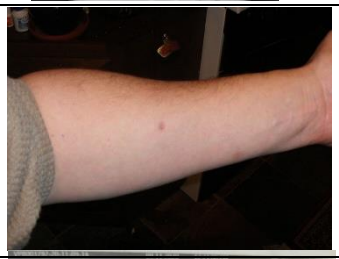
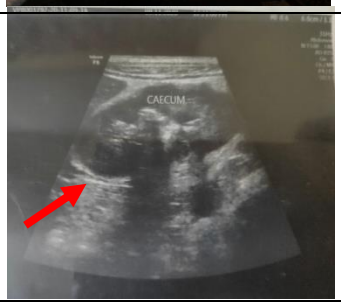
Child was admitted and evaluated for ITB and CD.

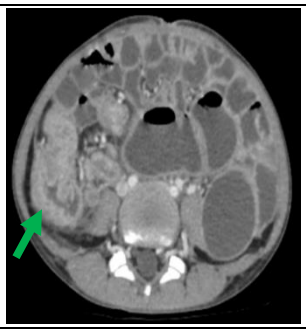
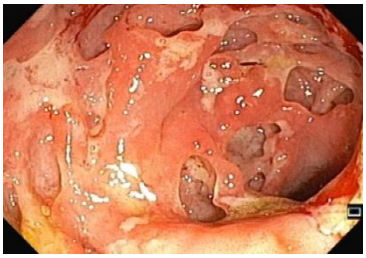


Comparing the MO (Modus Operandi) of the two suspects with the patient's symptoms

Features	ITB	CD	Patient
Family history	++	+	No
Duration of symptoms	6 months	Longer – up to 4-5 years	5-6 years
Intestinal symptoms	++	++	++
Perianal lesions	--	+	--
Extraintestinal symptoms	--	+	--
Ascites	+	--	--
Growth failure	+	+++	+++

Further Interro(Investi)gations.

Investigation	Result	Pictorial Evidence (If any)
Chest X-Ray	Normal	
Mantoux	Negative	
USG Abdomen	• Grossly thickened and pulled up caecum • Thickened terminal ileum with ileocolic, right colic and paracolic lymphadenopathy more suggestive of ileocecal TB than CD	

CECT abdomen	• Circumferential wall thickening in the distal ileum and caecum with multiple necrotic nodes	
Colonoscopy	• Ileocolic ulceration with pseudo polyps and ileocecal valve involvement suggestive of TB • However, possibility of CD couldn't be ruled out	

Act 7 – The Culprit

After these investigations, the diagnosis was within reach.

The incriminating evidence

Exhibit A - Colonic biopsy showed ulceration, caseous granuloma & granulation tissue formation indicating a stronger possibility of tuberculosis.

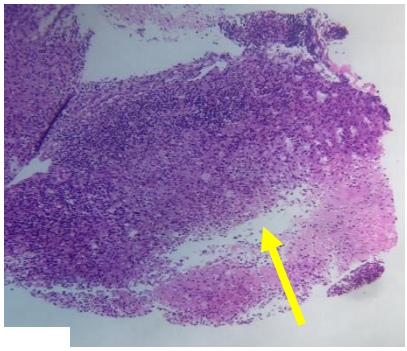


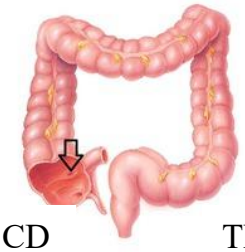
Exhibit B - CBNAAT report of biopsy specimen came as **Mycobacterium Tuberculosis** positive.

The boy was finally diagnosed to have ileocecal TB and started on Anti Tuberculosis Treatment (HRZE) to which he responded well.

Act 8 – The Archives

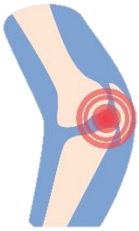
The following are some points to note when dealing with similar situations.

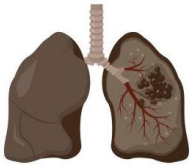
- Clinical features in both ITB and CD include constitutional GIT symptoms like diarrhea, hematochezia, abdominal pain & malabsorption.



CD TB

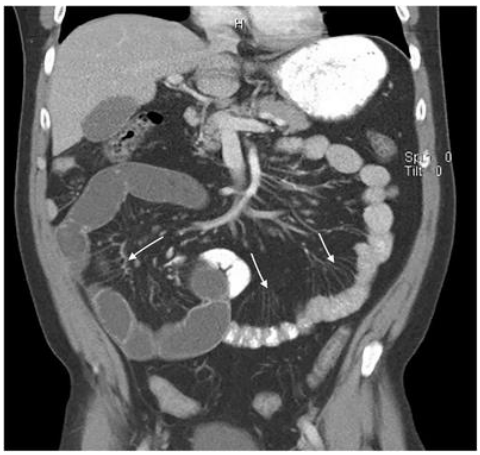
- Ileocecal region is the most common site affected in either condition, but CD can involve any portion of gastrointestinal system.

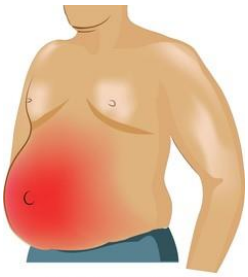




- Extra-intestinal manifestations such as arthritis and sclerosing cholangitis occur predominantly in CD while involvement of primary sites like pulmonary or lymphadenopathy is seen in TB.

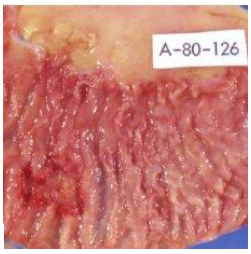
- "Vascular jejunization of the ileum" or the "comb" sign is typically seen in CD.





- Presence of ascites and caseating lymph nodes suggest abdominal TB.

[NB – Don't confuse "belly" with ascites.]



- On endoscopy, transversely placed ulcers, hypertrophic lesions, are frequent in ITB.

- Aphthous or longitudinal deep fissuring ulcers and cobblestone appearance are more typical of CD. Skip lesions in the colon are significantly frequent in CD.

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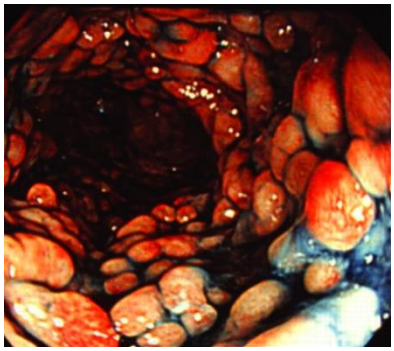

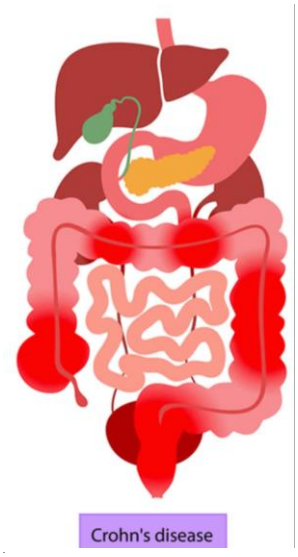

- Granulomas in TB are numerous, large and confluent, especially in the submucosa while those of Crohn's are fewer, smaller, non-confluent, & never caseating

Epilogue

- In children presenting with vague abdominal pain, weight loss, low-grade fever, and abdominal distension suspect TB & CD.
- Lack of gold standard investigation techniques makes the job even harder.
- In ambiguous cases investigations like PCR, CBNAAT should be done.
- Wherever possible, microbiological diagnosis is highly justified before the start of a course of therapy.
- Response to treatment indirectly confirms diagnosis.

Further read

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3. Larsson G, Shenoy T, Ramasubramanian R, et al. Routine diagnosis of intestinal tuberculosis and Crohn's disease in Southern India. World J Gastroenterol. 2014;20:5017-24.
4. Singh SK, Srivastava A, Kumari N, Poddar U, Yachha SK, Pandey CM, et al. Differentiation between Crohn disease and intestinal TB in children. J Pediatr Gastroenterol Nutr. 2017 May;64(5):703-7.
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Fatal sepsis and meningitis in an immunocompromised patient - The miscreant claims a life

Authors: Kaizen's of microbiology
Correspondence: Dr. Nirmal George

Synopsis

- 52-year-old diabetic ♀ (long standing not on treatment)
- Fever x 2 days, bleeding PV and urinary incontinence x 1 day
- Chronic liver disease (CLD) & Portal hypertension – Hepatitis C induced
- Diagnosed rheumatoid arthritis – on improper treatment with dexamethasone & hydroxychloroquine
- Patient was staying alone, and was found unconscious lying in the bathroom in the morning.
- Partially recovered with altered sensorium after regaining consciousness

In the hospital

- Febrile with elevated blood pressure
- Restless with neck stiffness
- Extensor plantar reflex
- Intensive care admission with ventilatory support in view of impending respiratory failure
- Insulin infusion started and plasma glucose attained reasonable control
- Empirical treatment was initiated with parenteral Ceftriaxone 2 gm I.V BD + Vancomycin 1 gram in 100 ml normal saline 8th hourly (considering pneumococci) + Acyclovir 500 mg I.V. 8th hourly (stopped after CSF study)
- **Investigations**
- Liver function tests showed serial elevations in
- AST: 272, 1937, 2993, 3225
- ALT: 129, 770, 1312, 1339

Normal CT brain

CSF after initiation of treatment

- Leukocyte count: 145 cells,
- Differential count, Neutrophils:9, lymphocytes: 91,
- Protein-260.8 mg/dL, Glucose - 36 mg/dL

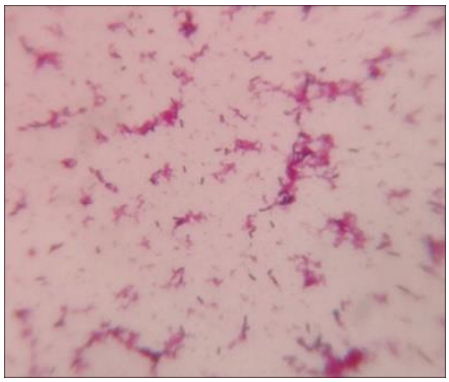
Elevations

- Total leukocyte count (14,500 cells) with neutrophilic predominance (76%)
- C-reactive protein – 47.4→ 64.7→ 30.6

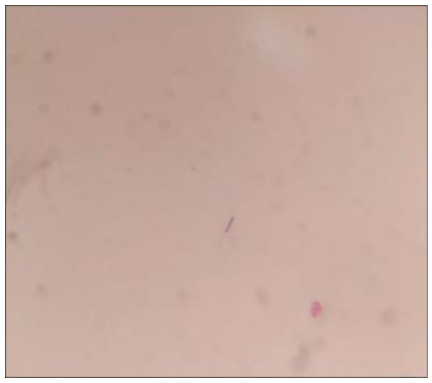
- Procalcitonin (2.28)
- Erythrocyte sedimentation rate (115 mm in the 1st hour)
- Plasma glucose – 306 mg/dL

What the Kaizen's dug up!

- Growth from blood was detected using automated system for detecting microorganisms in blood and other sterile body fluids and was the organism was identified and confirmed by automated system.

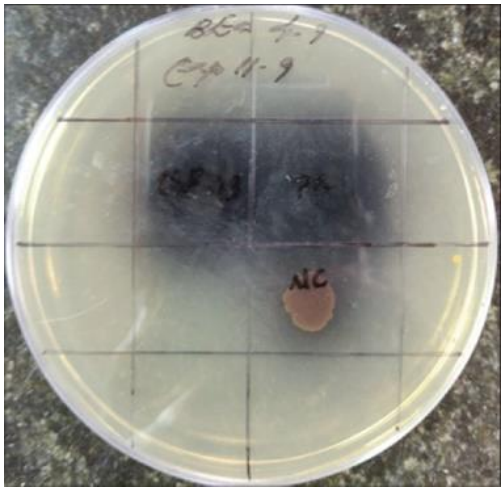


Direct blood smear showed gram + non sporing bacilli

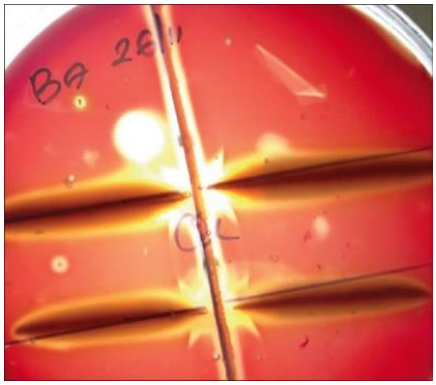


Direct CSF smear showed gram + non sporing bacilli

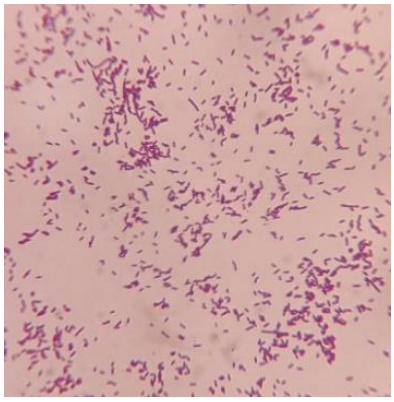
Blood agar – smooth translucent colonies with narrow β hemolysis



Bile aesculin agar hydrolysis



Positive Christie, Atkins and Munch–Peterson test



Colony smear

Hanging drop preparation

Tumbling motility

Overnight broth culture at 22^{o}C

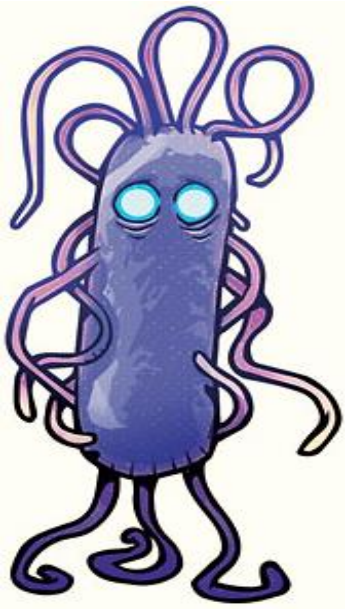
Other positive tests

- Catalase test
- Methyl red test
- Voges-Proskauer test
- Fermentation of glucose and maltose without production of gas

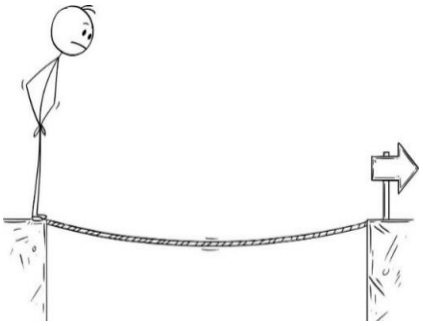
Negative test

- Oxidase test
- **All findings point to one direction – *Listeria monocytogenes* induced meningitis and septicemia**
- Organism was sensitive to β lactam antibiotics (Penicillin, Ampicillin), Aminoglycosides, Tetracycline, Erythromycin, Cotrimoxazole, and Rifampicin
- Initiated on Ampicillin 2 gm I.V 4th hourly and gentamicin 80 mg I.V in 100 ml normal saline 8th hourly → reduction in fever
- But was clinically deteriorating
- Repeat CT brain– non communicating hydrocephalus → death after 3 days

Discussion



- Annual global disease burden – 1600 cases & 260 deaths
- Perinatal infections - miscarriage, premature delivery, amnionitis and neonatal infections
- Indian scenario – Genital listeriosis (common presentation)
- Gram +, non-sporing, facultatively anaerobic bacilli
- Non motile >37^{o} C, motile at lower temperatures
- Transmission through food (diary, frozen and refrigerated food materials – high virulence)
- Risk factors – Immunocompromised states (pregnancy, extremes of age, uncontrolled diabetes mellitus, immunosuppressants and malignancies)
- In immunocompromised – Sepsis, meningitis or endocarditis



Challenges with listeria

- Underdiagnosed and underreported - especially in India
- Long incubation period
- Visually similar to diphtheroid, streptococci & pneumococci
- Facultative intracellular pathogen, hence commonly used antimicrobial agents are ineffective
- Variable incubation period (3-90 days)
- Ability to cross barriers (placental & BBB)
- High rates of mortality and morbidity (CNS infections & septicemia)

Red flags to suspect Listeria

- Immunocompromised states
- Elderly (>55 years)
- Pregnancy
- Presenting with CNS infections or disseminated infections not responding to empirical treatment

Treatment

- Ampicillin (8-12 grams daily 4^{th} – 6^{th} hourly) - drug choice
- Gentamicin or Co-trimoxazole – 2^{nd} choice
- Minimum duration of treatment – 3 weeks

Saving the patient depends entirely on microbiological identification and clinical acumen.

Recent United Kingdom guideline recommends prescribing ampicillin empirically in patients aged above 55 years with suspected meningitis or sepsis considering Listeria.

Conclusion

When in doubt of *L. monocytogenes*, consider addition of ampicillin or gentamicin or a combination of both!

Kaizen's of microbiology:

1. **Ashna Ajimsha, Junior Resident**
2. **Ivy Viswamohanan, Associate Professor**
3. **Ganga Raju Krishna, Assistant Professor**
4. **Ashish Jitendranath, Professor**
5. **Ramani Bai, Professor & Head**

Further read

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5430879/#:~:text=In%20hanging%20drop%20method%2C%20the,(2.5%20%C2%B5g%2Fml)
2. https://www.ncbi.nlm.nih.gov/books/NBK534838/

Reporting from the front

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Cavalry: Dr. Ansar P P, Dr. Kingini K, Dr. Anila T
Artillery: Dr. Praveen Keshav
Signals: Dr. Manoj P
Correspondent: Dr.Vivek George

The Lull……

- 72-year lady admitted for residual thyroidectomy.
- Evaluated for anesthesia fitness
- Symmetrical, bilateral upper and lower limb weakness with hyporeflexia
- Neurology opinion: Guillain Barre Syndrome. (GBS)
- Admitted in ICU
- Treated with IV immunoglobulin and supportive measures.

Before the storm

- Routine Clinical examination - Hepatomegaly
- Referred for USG - suggestive of a hepatic mass
- CECT advised
- **CECT abdomen:** A large, well defined, iso-hypodense lesion measuring 15 x 11.2 x 15.2 cm with non-peripheral arterial hyperenhancement and washout in the venous and delayed phase.
- There were a few non enhancing necrotic areas within.
- The lesion was causing displacement of the middle and the left hepatic veins and IVC to the left without any evidence of encasement or intravenous thrombosis.
- No portal vein thrombosis.

The numbers

Total bilirubin	0.85mg%
Direct bilirubin	0.17mg%
SGOT	65 IU/L
SGPT	43 IU/L
Alkaline phosphatase	140 IU/L
Total protein	9.6g%
Albumin	3g%
Prothrombin time	13 secs
α- Fetoprotein	**386 IU/L (Normal < 7 IU/L)**

Patient recovering from GBS with IV immunoglobulin and supportive measures. The enemy is yet to be tackled.

The War room meeting

Cavalry: Should we go in for the kill (**hepatectomy**)

Signals: Too risky, there can be serious, even fatal collateral damage (**peri-operative complications**). The enemy is well entrenched.

Artillery: How about cutting the supply lines? (**TACE***)

Cavalry: Abrupt cut off may release the suicide squad (**Tumor lysis syndrome**)

Signals: The situation on the ground (**GBS**) will then worsen.

Artillery: Let's lay a gradual siege (Targeting the right anterior sectoral and right posterior sectoral feeders sequentially over an interval of 1 month.)

Cavalry: Roger

*Trans Arterial Chemo-Embolization

Reports from the front line

	Day 1 (Post TACE-1)	Day 32 (Post TACE-2)
Total bilirubin	0.90 mg%	1.9 mg%
Direct bilirubin	0.80 mg%	1.1 mg%
Indirect bilirubin	0.10 mg%	0.8 mg%
SGOT	75 IU/L	525 IU/L
SGPT	44 IU/L	112 IU/L
Alkaline phosphatase	90 IU/L	150 IU/L
Total protein	9 g%	7.6 g%
Albumin	3 g%	2.3 g%

Post TACE syndrome	NIL	YES (managed conservatively)
Tumor lysis syndrome.	NIL	NIL
Post TACE Imaging (1 month)	large HCC in the right lobe with post TACE changes **(Fig.1)**	large HCC in the right lobe of liver with heterogenous, patchy distribution of lipiodol. **(Fig.2)**
LR-TR	Viable disease	Viable tumor
mRECIST	Stable disease	Stable disease

- Few supply lines still intact (The HCC had predominant extra-hepatic feeders from right lower intercostal and right inferior phrenic arteries.)
- Post second TACE, GBS settled, Patient physically fit for surgery.

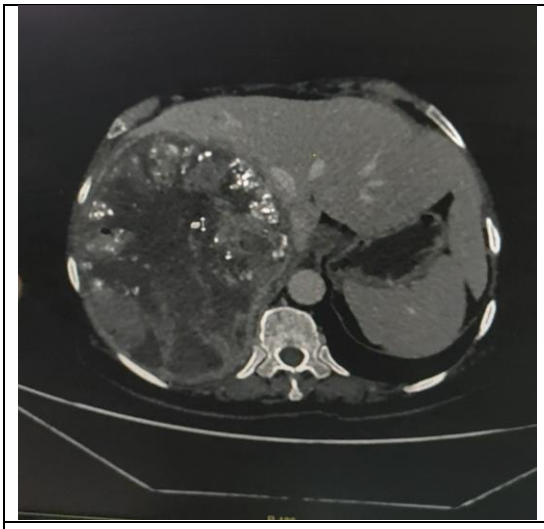


Fig1

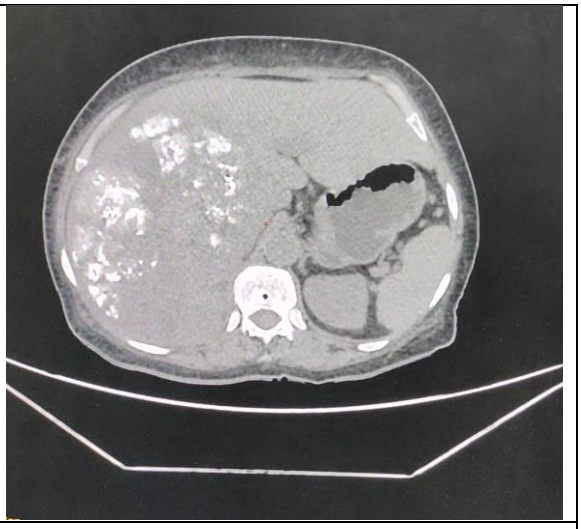
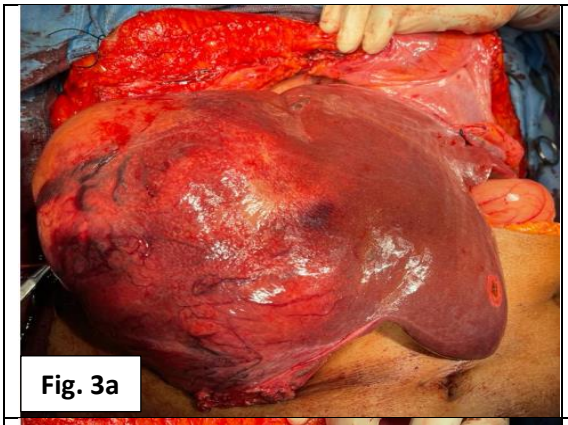


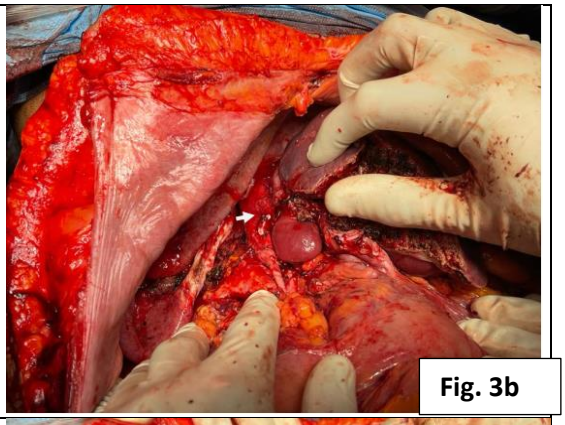
Fig 2

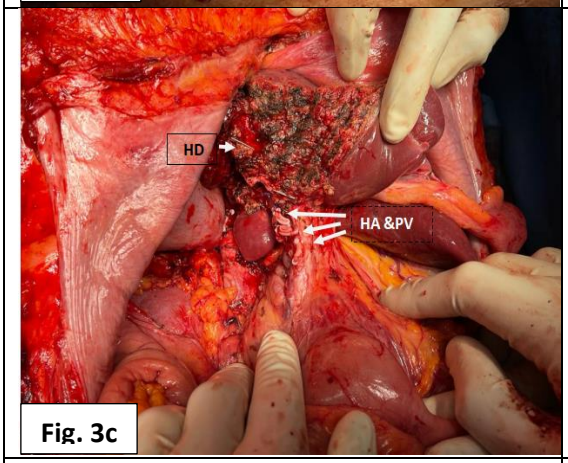
For Description Refer Table 1

GOING IN FOR THE KILL-THE SURGICAL STRIKE

- A Mercedes Benz incision was placed.
- Portal dissection with Inflow to the right lobe (right hepatic artery, right branch of portal vein and finally right hepatic duct) were identified , dissected and ligated separately.
- Outflow tract (right hepatic vein) was closed using 60mm vascular stapler.
- Parenchyma was divided in the end and right hepatic duct was identified and ligated within the parenchyma.
- Post operative period uneventful







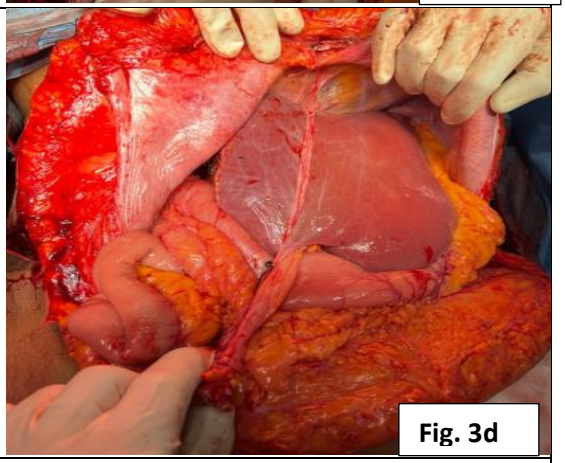


Figure 3a After complete mobilization and vascular ligation of liver	**Figure 3b Right hepatic vein (white arrow) and multiple spigelian vein between liver and IVC seen ligated.**
Figure 3c: Completed hilar dissection. (Right hepatic artery, portal vein clipped at porta. Right hepatic duct clipped along parenchyma.)	**Figure 3d: After parenchymal transaction.**

REVEALING THE ENEMY

Tumor Size
19x15x10 cm (2080 gms)

Type
HCC Clear cell variant-Grade 2

Stage
pT1b N0 M0.

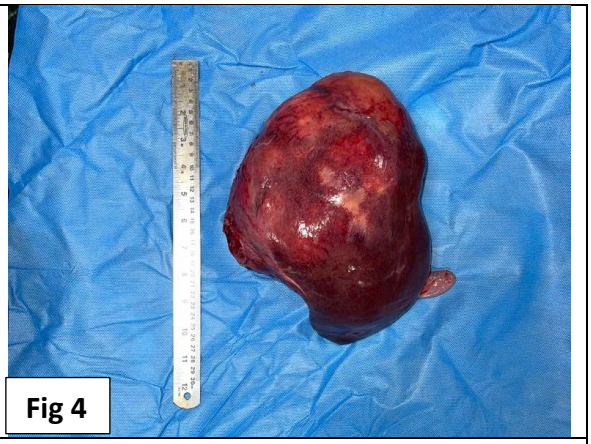


Fig. 4 Right Hepatectomy specimen sent for Histopathology

FLASHING THE VICTORY SIGN

- Follow up at 6 months post surgery
- LFT -Normal
- α- fetoprotein within normal limits and
- Imaging: No evidence of any enhancing lesion in liver/ elsewhere.

EPILOGUE

- Hepatocellular carcinoma is the most common primary liver malignancy[1]. Cirrhosis is the most important risk factor with 80% of HCC occurring in cirrhotics.
- However upto 25% of patients may have no cirrhosis or any other risk factors as in our case.
- GBS has been associated with various malignancies including HCC[2].
- The pathogenesis of GBS in HCC is unknown but it is believed to be the result of aberrant humeral and cellular immune responses to the peripheral nervous system with multiple triggers eg: malignancy, surgery etc.
- Our case was further complicated by the fact that the active GBS made the anesthesia for immediate hepatectomy more complicated.
- To allow for the musculature to recover, surgical management was deferred and the interim period to complete recovery was managed with TACE.
- This helped to contain the disease and prepare the liver for optimal resection.
- Several studies have proved that the overall disease free interval and survival benefits are better with TACE followed by liver resection[3,4,5,6,7]
- 6 month FU was uneventful with normal imaging and AFP levels underlining the significance of the management strategy.

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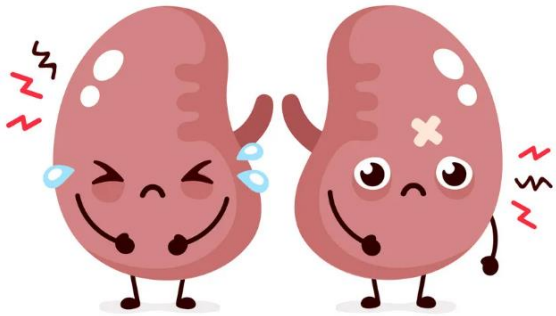
Theoretical extravaganza

Drug use in chronic kidney disease – Pharmacological considerations

Author & correspondence: Dr Nirmal George

Problem statement:



- Renal dysfunction & drug use are common
- 50% drugs or its metabolites are eliminated by kidneys
- 20% hospitalized patients have renal dysfunction.
- 30% adverse drug reactions (ADR) are kidney related

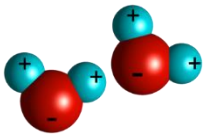
General statement: 'Renal dysfunction affects pharmacokinetics to greater extend than pharmacodynamics'

Pharmacokinetics – What the body does to the drug!

Pharmacodynamics – What the drug does to the body!

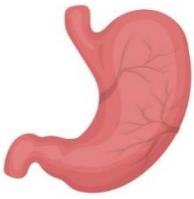
I. Renal dysfunction induced alterations in pharmacokinetics

a. Absorption - General principles



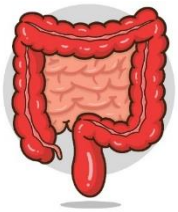
- Charged molecules have difficulty in crossing any membranes since membranes are made of lipids

Acidic drugs are absorbed from stomach



- Since they remain unionized in the acidic medium of the stomach

Basic drugs are absorbed from intestine



- Since they remain unionized in the alkaline medium of intestine

Absorption: Change 1

- In renal dysfunction, there is increase in levels of urea which gets converted to ammonia. Ammonia will increase the pH of stomach which will result in reduced absorption of acidic drugs. This is further accentuated in people who are on concomitant medications that increase the gastric pH (PPI, H_2 blockers, antacids).

Absorption: Change 2

- Renal dysfunction cause fluid retention which leads to edema of the gastrointestinal mucosa which reduces absorption of drugs e.g., bioavailability of furosemide reduces from 50% to 10% in patients with gastrointestinal edema.

Absorption: Change 3

- Reduced excretion of toxic waste products damages the gastrointestinal mucosa hence there is reduction of absorption of drugs from Gastrointestinal tract.

Absorption: Change 4

- Some drugs are metabolized before it reaches the systemic circulation. This is known as first pass metabolism or first pass effect. This is done by liver and intestinal epithelial cells.

Activity of the drug metabolizing enzymes is inhibited by renal dysfunction which increases the plasma concentration of drugs which is often misconceived as due to reduced excretion of drugs in renal dysfunction.

b. Distribution – General Principles

Volume of distribution (Vd): It's a hypothetical space in which the drug has to be distributed to attain the concentration in plasma.

$$Vd = Amount\ of\ drug\ administered / plasma\ concentration$$

As a general rule:

- '**Free drug or the unbound drug is the one that produces the pharmacological effect**'
- Drug with high tissue binding would have low plasma concentrations, hence high Vd. So, when Vd increases, therapeutic effect of most drugs reduces.

Changes in distribution

Change 1

- In renal dysfunction, fluid content of the body increases. This will increase the Vd of water soluble and protein bound drugs. This will cause a reduction in free drug concentrations and their **therapeutic failure**

Change 2

- Alterations in plasma proteins
  - Urinary loss of albumin
  - Altered structure of albumin
  - Endogenous acids competing with drugs for plasma proteins
  - E.g., Phenytoin toxicity in renal dysfunction can occur due to reduced plasma protein binding of phenytoin

Change 3

Alterations in tissue binding:

- e.g., tissue binding of digoxin is reduced in renal dysfunction hence higher rates of toxicity.

Change in distribution that occurs during Dialysis

- Dialysis produces contraction of cell mass which increase the fraction of body water.
- Volume of distribution of water-soluble drugs increases.
- Hence, there is reduction in free drug and reduction in therapeutic efficacy.

Similar scenario is seen in patients with oliguria

Changes in free drug concentration of some commonly used drugs

Drug	**Change in concentration**
Ceftriaxone	free drug ↑ by 100%
Doxycycline	free drug ↑ by 133%
Methotrexate	free drug ↑ by 12%
Phenytoin	free drug ↑ by 115%
Sodium valproate	free drug ↑ by 188%
Warfarin	free drug ↑ by 100%
Clonidine	free drug ↓ by 14%

c. Metabolism – General principles

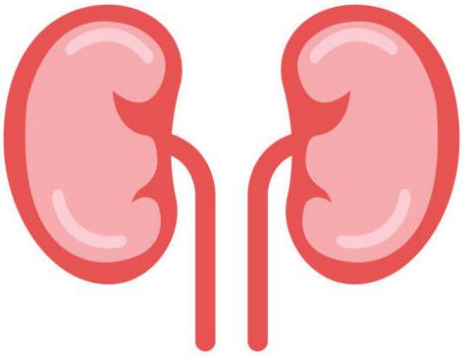
- Liver is the major metabolizing organ in our body
- Unbound drug undergoes metabolism

Changes in metabolism

Change 1. In renal dysfunction, there is loss of albumin in urine.

- This will result in increased levels of free albumin bound drugs
- This will increase the metabolism of these drugs
- Therapeutic failure

Change 2. Toxic drug metabolites of drugs are eliminated by the kidneys



- Renal dysfunction can cause accumulation of toxic metabolites and subsequent toxicity

Change 3

50% of drugs are metabolized by CYP3A4/5 enzyme of the liver. The effects of renal dysfunction on the enzyme complex is complex and not well-studied.

- The rest of the metabolizing enzymes and drug transporters' activity is reduced by renal dysfunction, proportional to the degree of renal dysfunction.
- These effects are less pronounced in acute kidney injury (since liver is spared in AKI, serum creatinine does not correspond to degree of renal dysfunction in these patients).
- **Potential dosing errors can occur in these patients if prescribed according to Serum creatinine**
- Based on these data a conclusive statement on the alterations in drug metabolism by various enzymes cannot be made clearly! Our bad!

E.g. Morphine is metabolized by the liver to morphine-6-glucuronide which is excreted by the kidneys. In renal dysfunction, morphine-6-glucuronide accumulates, resulting in toxicity.

d. Effects on excretion of drugs

- For drugs primarily eliminated by kidneys, Chronic renal failure can cause reduction in excretion and subsequent toxicity.

II. Renal dysfunction induced alterations in pharmacodynamics

- **Pronounced for antimicrobial agents**
- **Lower rate of elimination = longer duration of action = better coverage/ higher toxicity**

Assessing renal dysfunction

1. **Cockroft Gault Equation (Age old, new versions available)**

$$eGFR = (140 - age)\ x\ Ideal\ body\ weight / (Serum\ creatinine\ x\ 72)$$

Ideal body weight = weight + (2.3 kg x each inch over 5 feet); Weight = 50 kg for males, 45.5 kg for females. eGFR values should be multiplied with 0.85 in females.

2. **Chronic kidney disease-epidemiology collaboration (CKD-EPI)**

eGFR= 141 x min (S.Cr/κ, 1) $^{\alpha}$ x max (S.Cr/κ, 1) $^{-1.209}$ x 0.993 ^{age};

κ=0.7 (female), 0.9 (male), α=-0.329 (female), -0.411 (male)

eGFR value obtained is multiplied by 1.018.

Online FREE GFR calculator is available at https://www.mdcalc.com/calc/3939/ckd-epi-equations-glomerular-filtration-rate-gfr

Drug dosing in CKD

- **Loading dose is necessary to attain steady state plasma concentration rapidly.**
- Goal- produce plasma concentrations similar to normal individuals (trough, peaks and steady state concentration).
- **Loading dose** = Vd x Cmax x Ideal body weight, Vd: volume of distribution, Cmax: steady state concentration. Since Vd is higher in CKD, loading dose will be larger.
- **Maintenance dose**
- Maintenance dose = D x Q; Q= 1-[fe (1-KF)], D: normal dose, Fe: fraction of drug eliminated unchanged by kidney & KF: patients GFR/120.
- **Determining the frequency of drug dosing**
- T= Tn/Q, Q= 1-[fe (1-KF)]

In a nutshell, patients with CKD requires higher loading dose, lower maintenance dose or lower frequency of drug dosing

3. **Rough estimates in general practice**

e-GFR	Rough dosing
50-70 % of normal	70% of adult dose
30-50 % of normal	50% of adult dose

10-30 % of normal	30% of adult dose
5-10 % of normal	20% of adult dose

"These dose reductions are not applicable in all patients and not for all drugs as well. It is necessary to use this practice with utmost caution".

4. **Assessing renal function in paediatric age groups**

eGFR = 39.8 x (height / S. Creat) $^{0.456}$ x (1.8/Cystatin C) $^{0.418}$ x (30/BUN) $^{0.079}$ x (height/1.4) $^{0.179}$

5. **Assessing renal function in acute kidney injury (AKI) and drug dosing in AKI**

Since serum creatinine values change serially in AKI, formulas used to calculate e-GFR is not applicable in AKI. Patients with AKI would be over hydrated; hence the volume of distribution would be higher. Since loading dose depends on Vd, Ld would be higher in these patients. A 25% higher loading dose and a near normal maintenance dose is recommended.

Kinet GFR = [(150-age) x weight/ Serum Creatinine 2] x [1-(Cr2-Cr1)/(t2-t1) x (24/200)].
Patients with AKI

6. **Drug dosing for patients undergoing hemodialysis (HD)**

- Some amount of kidney function is preserved
- Dialysis removes drugs from systemic circulation.
- This depends on diffusion of the drugs, surface are of the dialyzing membrane and size of the pores of the dialysing membrane.

Clearance by hemodialysis (ClHD) = Fu x Clurea x (60/Molecular weight of the drug)
Fu is the fraction of unbound drugs, Cl urea is the clearance of urea, MW is the molecular weight of the drug.

Drug dosing in RRT

Calculating clearance in patients receiving CRRT is very complex. The simple and easy method is to estimate the clearance of creatinine since drug removal follows similar pattern as creatinine.

Commonly used drugs & dosing recommendations

1. Paracetamol - eGFR < 10/HD – 8th hourly
2. Aspirin - eGFR < 10 - Avoid
3. Cefixime - eGFR 10-50 - Dose ↓ to 75-100%, eGFR <10/HD - Dose ↓ to 50%
4. Cetirizine - eGFR <10/HD - Dose ↓ to 50%
5. Chlorthalidone - eGFR <50 – Avoid
6. ciprofloxacin - eGFR 10-50 - Dose ↓ to 50-100%, eGFR <10/HD - Dose ↓ to 50%
7. Enalapril -eGFR 10-50 - Dose ↓ to 50-100%, eGFR <10/HD - Dose ↓ to 25%
8. Metformin - eGFR 10-50 - Dose ↓ to 50% to avoid, eGFR <10 – Avoid
9. Clopidogrel & Ampicillin – no change in dose

Further read:

1. Brenner & Rector's The Kidney 10th edition

2. https://www.ncbi.nlm.nih.gov/books/NBK560512/

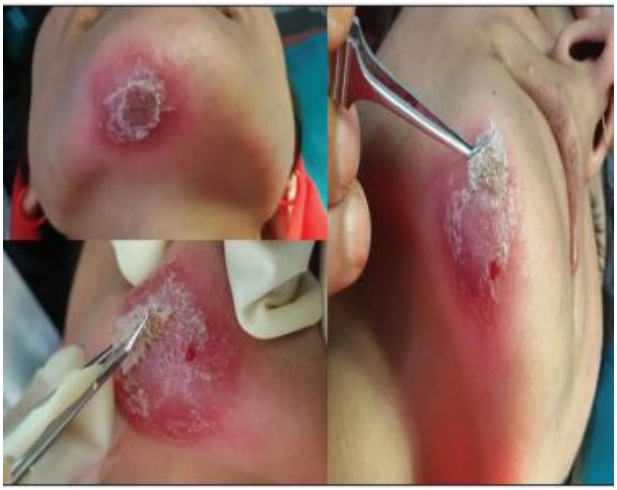
Manifestation of a rare disease – Can it be due to post COVID inappropriate immune reconstitution?

Authors: Dr Priya Prabhakaran, Dr Simi S M, Dr Devan Prakash, Dr Suja V

Correspondence: Dr Nirmal George

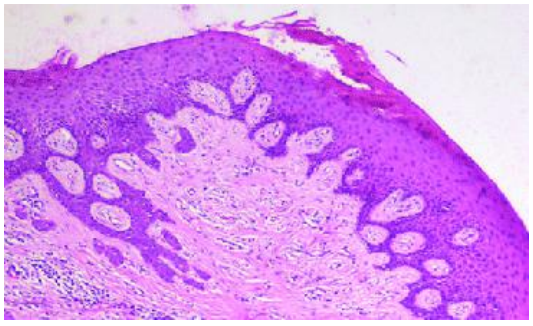
Synopsis: A forest watcher presented with erythematous plaques on exposed areas of the body with hyperpigmented scalp with a positive carpet track sign. The present case describes the challenge in diagnosing the manifestation of rare disease in post COVID era which was managed successfully.

The case report



- 46-year-old ♂ forest watcher from Kulathupuzha
- Presented with multiple well defined erythematous plaques with adherent scales and peripheral atrophy on face, trunk and arms x 1 year
- Lesions were photosensitive
- Hyperpigmentation of scalp with surrounding atrophic plaques
- Carpet track sign + from lesions

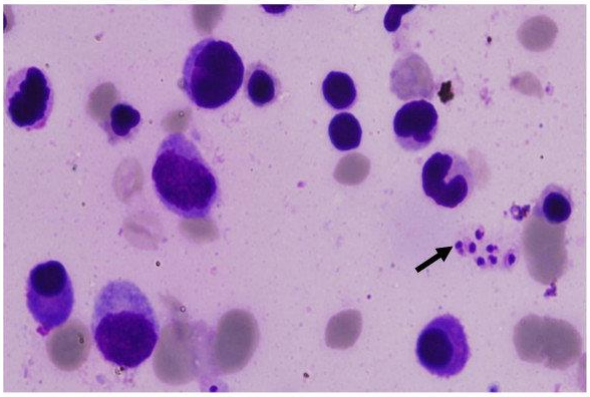
Provisional diagnosis:
Discoid Lupus Erythematosis



Investigations

Skin biopsy for histopathology

- Pseudoepitheliomatous hyperplasia
- Lymphocytic & plasma cell infiltration in the dermis



- Cytology – Leishman Donovan bodies

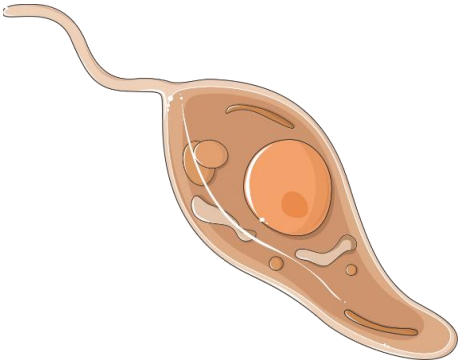
Diagnosis

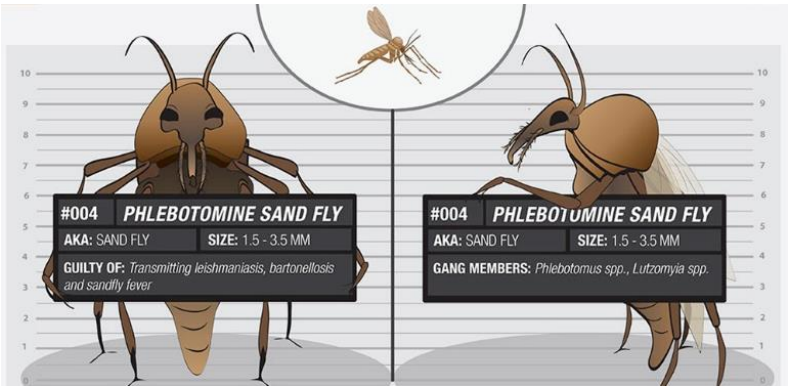
- **Cutaneous leishmaniasis**
- Patient was initiated on Itraconazole 200 mg BD x 4 weeks and had good response to treatment

Discussion

- Leishmaniasis is a neglected tropical disease caused by Leishmania spp.
- Vectors are female sandfly of Phlebotomus (old world) and Lutzomyia (new world) genus.
- Organism survives as promastigotes within sandfly and amastigotes within the host.
- Animals and humans act as reservoirs of leishmania.

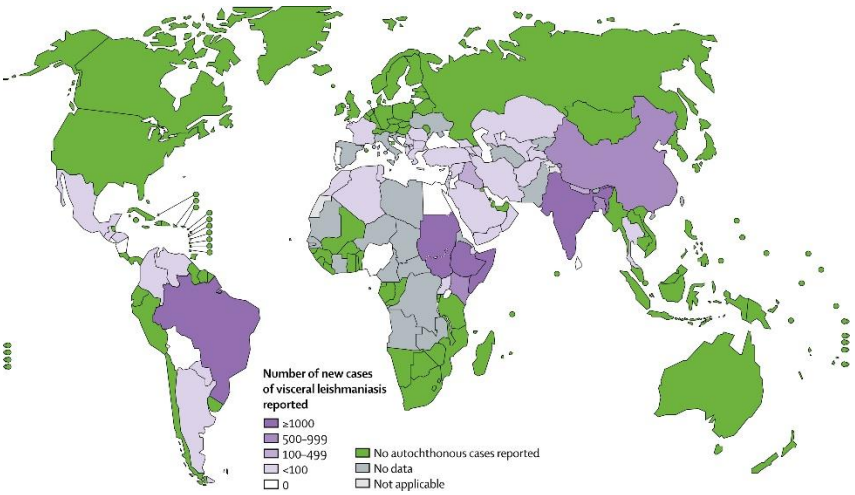
The perp and its ride!



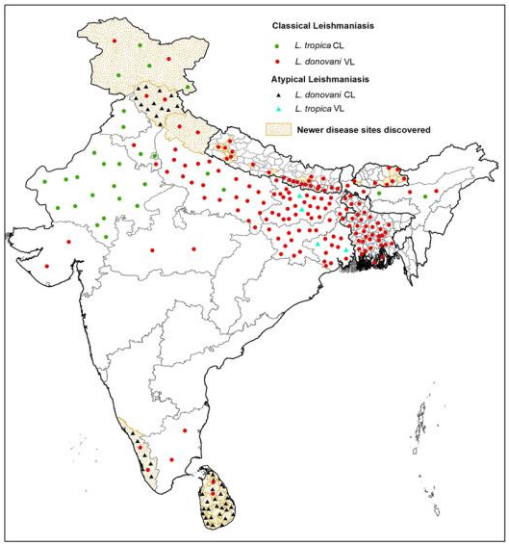


Epidemiology:

- Globally **1.5 to 2 million new cases** occur annually and **310 million are at risk**.
- Mucocutaneous and visceral leishmaniasis contributes to **70,000 deaths annually**.
- **18%** of global visceral leishmaniasis is from **India**.



The Indian Scenario



In **India** Leishmaniasis is endemic to

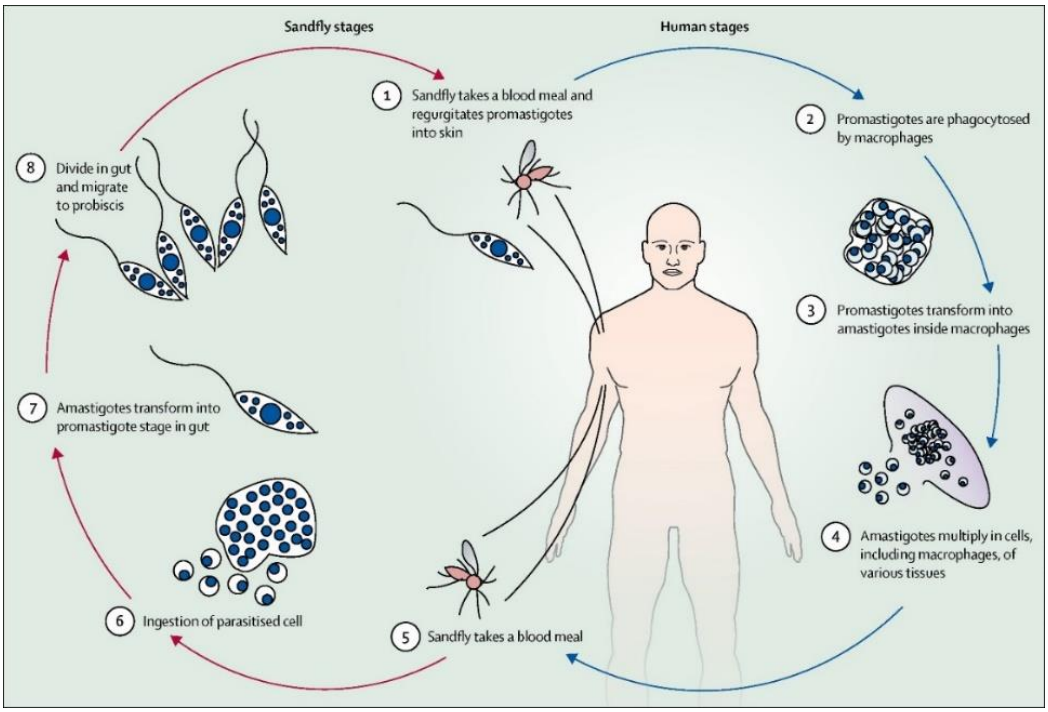
- Bihar, West Bengal, Jharkhand, Uttar Pradesh
- Northwestern India surrounding the Thar desert
- Pockets in Himachal Pradesh and Kerala
- L.donovani zymodene mon-37 strain produce leishmaniasis in Kerala

Incubation period: 2 weeks to 2 months for cutaneous leishmaniasis and 2 months to 2 years in other types.

Risk factors

- Low socio-economic status
- Malnutrition & immunosupression
- Human incursion into the forest (present case)

Life cycle



Types

1. **Cutaneous:** Involves epidermis and dermis
2. **Muco-cutaneous:** Involves mucocutaneous junction
3. **Visceral:** Liver and spleen are the affected organs

Cells involved: Macrophages

Six similar cases of cutaneous leishmaniasis were reported from our Institution after the COVID-19 pandemic. In a person with normal immune response, cutaneous leishmaniasis does not manifest as disease. Could this be attributed to the persistent immunosuppression that is associated with covid 19?

- **Positive carpet tack sign might mislead the clinician into a diagnosis of discoid lupus erythematosus instead of cutaneous leishmaniasis**.

Investigations:

- Biopsy, aspirate from skin lesion, bone marrow, lymph node, blood or buffy coat, dermal scraping for Giemsa - Leishman Donovan bodies with kinetoplast
- PCR and culture in NNN medium
- Rk39 dipstick test in serum for visceral leishmaniasis

Treatment:

I. **Cutaneous leishmaniasis (Local therapy for < 4 lesions each lesion of < 4cm diameter)**
- **Intralesional agents** – Intralesional antimonial
  - Efficacy increased when combined with sodium stibogluconate, meglumine antimoniate or topical paramomycin (15%)
- **Systemic therapy**
  - Meglumine antimonate 20 mg/kg/ day x 20 days
  - Azole antifungals –
    - Itraconazole 200 mg BD x 4 weeks
    - Fluconazole 200 mg/day x 6 weeks
    - Ketoconazole 600 mg/day x 4 weeks
  - Liposomal amphotericin B

II. **Post kala-azar dermal leishmaniasis**
  - Liposomal amphotericin B
  - Miltefosine – 2.5 mg/kg/day x 28 days

III. **Mucocutaneous leishmaniasis**
  - Miltefosine & Liposomal Amphotericin B

IV. **Visceral leishmaniasis**
  - Miltefosine & Liposomal Amphotericin B

Conclusion

- The diagnosis of cutaneous leishmaniasis is often overlooked due to the rarity of the disease and the presentation.
- Erythematous scaly plaques on exposed skin should kindle a strong suspicion of cutaneous leishmaniasis especially in post COVID era.
- Positive carpet track sign has no value and is rather misleading to a diagnosis of discoid lupus erythematosis.

Further read:

1. **https://www.ncbi.nlm.nih.gov/books/NBK531456/**
2. **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9472198/**
3. **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6637076/**
4. **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9472198/**

Plumbing of a different genre! - Recreating obstructed biliary anatomy

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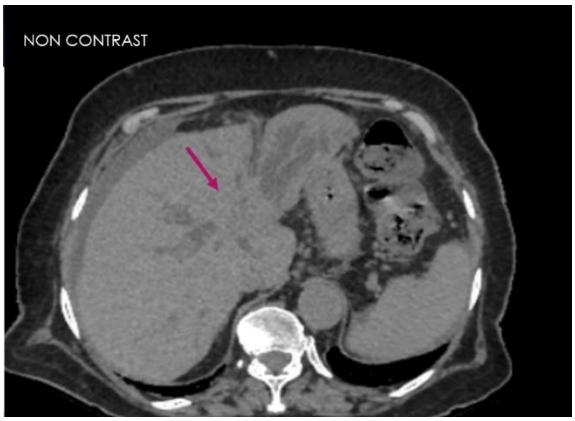
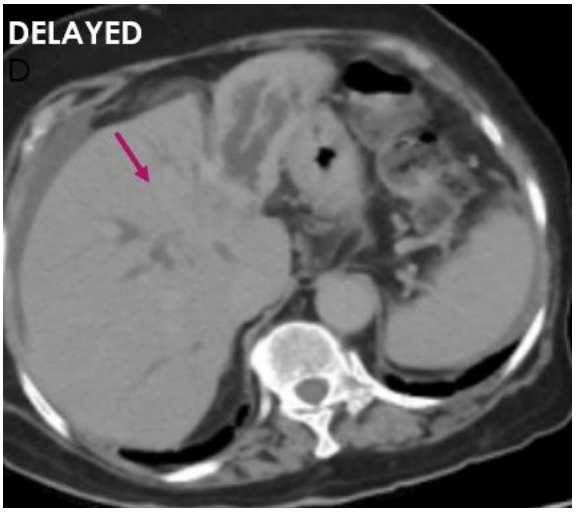
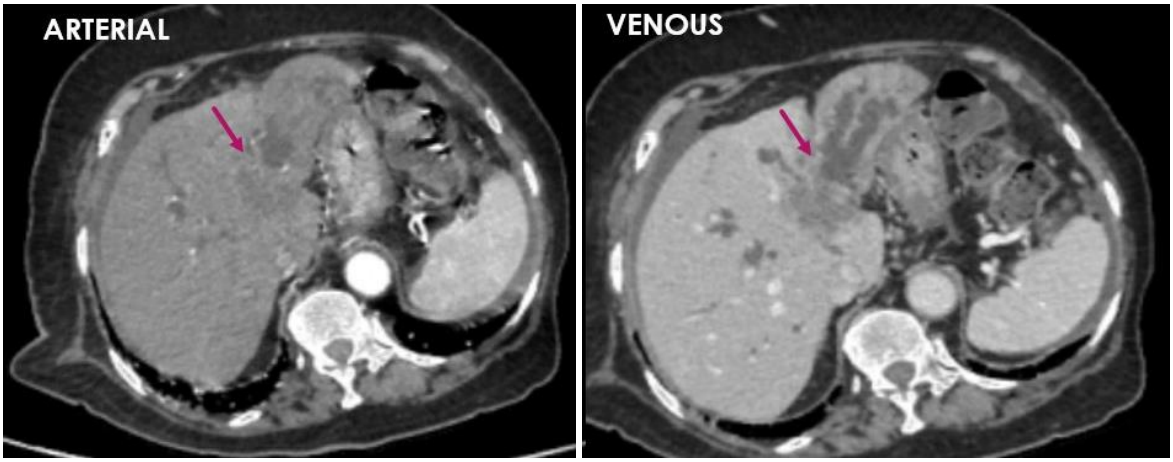
- 90 y/o ♀
- Jaundice, fever, abdominal pain x 1 month
- Clinical examination – icterus
- Investigations – deranged liver function tests
  - Elevated serum bilirubin & Ca 19.9
  - USG abdomen – mass lesion within the Common bile duct (CBD) at the porta hepatis with intrahepatic biliary radicle dilatation



- Non contrast Computed tomography (CT) showed an ill-defined isodense soft tissue lesion involving hepatic hilar region



- **Contrast enhanced computed tomography (CECT) abdomen**
  - Ill defined, intraluminal, progressively enhancing soft tissue density lesion
  - Involving predominantly left hepatic duct, extending into confluence, common hepatic duct and proximal right hepatic duct
  - Moderate intrahepatic bile duct dilation with infiltration into lobar parenchyma
  - Atrophy of left lobe and infiltration of left portal vein

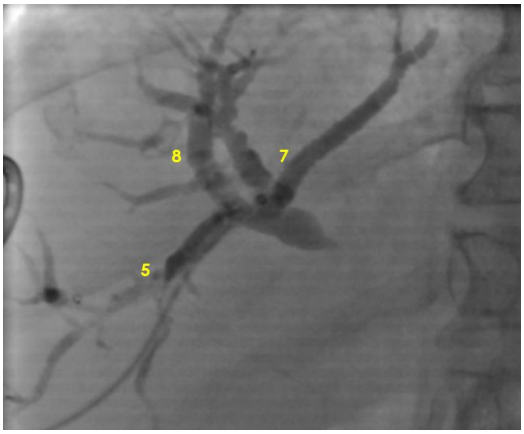


Diagnosis

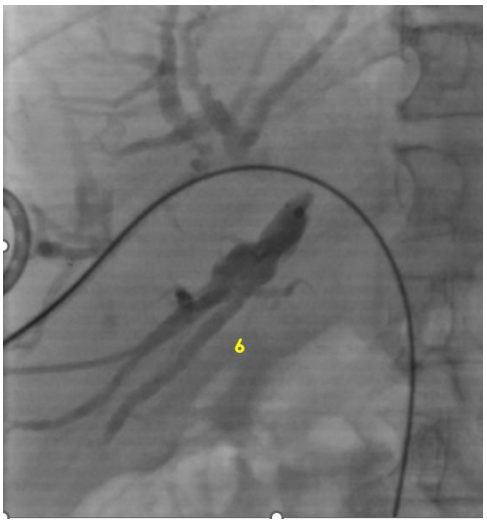
Malignant neoplastic lesion – likely hilar cholangiocarcinoma Bismuth Corlette type IV

Management in the hospital

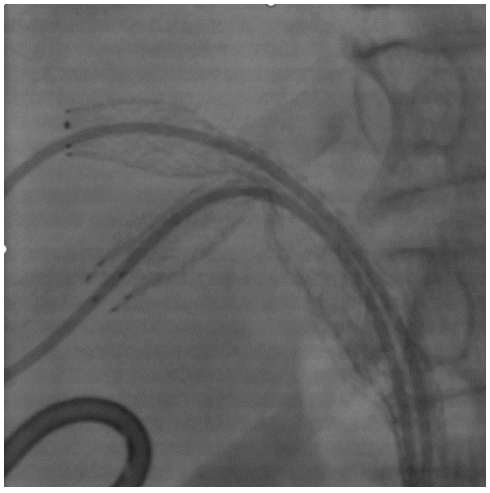
- Unresectable
- Palliative Percutaneous transhepatic biliary drainage (PTBD) was performed to
    - Facilitate biliary drainage,
    - Reduce serum bilirubin
    - Relief of symptoms of obstructive jaundice and cholangitis
- The patient underwent Palliative dual PTBD and a self-expanding metallic stent to drain right biliary system of segments 5, 7, 8 sectoral duct and segment 6 sectoral duct.



Pretreatment cholangiogram--anterior sectoral branches of right hepatic duct



Cholangiogram--segment VI branch draining into right hepatic duct

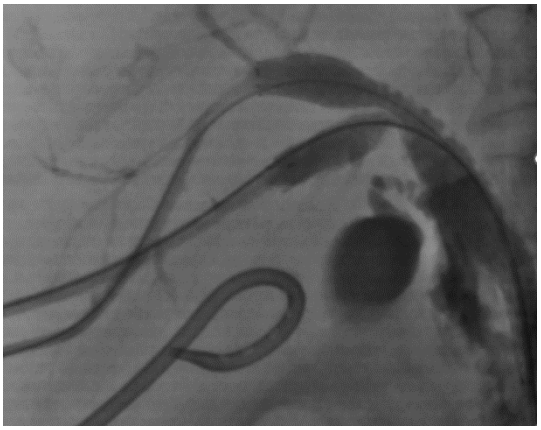


Post stenting

- Biliary catheters passed through which the self-expanding metallic stents were deployed

Post procedure check cholangiogram

- Free flow of bile into duodenum
- Relief of biliary obstruction
- Significant clinical improvement
- Reduction in serum bilirubin from 18 to 2 mg/dL

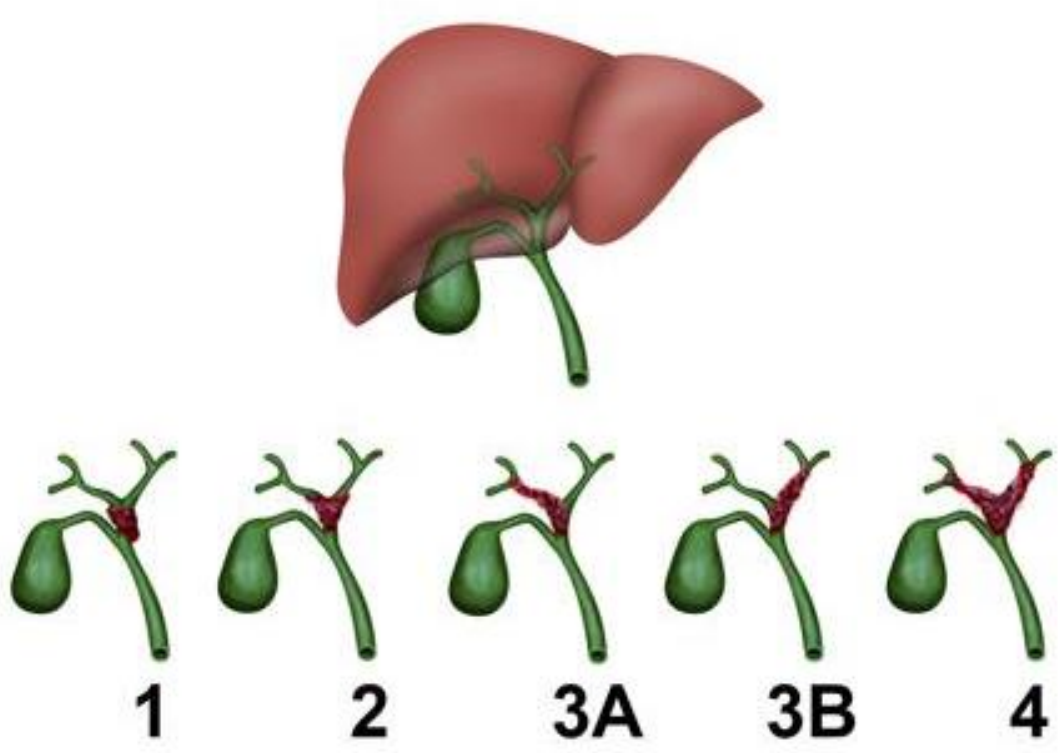


CHECK CHOLANGIOGRAM

- Normal biliary flow into duodenum
- Relief of biliary obstruction

Discussion

- Primary malignant tumor of biliary tract
- Location - bifurcation of common hepatic duct
- Computed tomography - ill-defined mass with intrahepatic biliary radicle dilatation
- Magnetic resonance cholangiopancreatography is superior to CT in delineated the extend of tumor and the location of biliary tree stricture
- Bismuth Corlette classifies hilar cholangiocarcinoma into four types



Type	Anatomical location & feature
1	Tumor below the confluence of the right and left hepatic ducts
2	Tumor extends to the confluence of the right and left hepatic ducts
3a	Tumor involving the confluence of the right hepatic duct
3b	Tumor involving the confluence of the left hepatic duct
4	Tumor involving the confluence of both right and left hepatic ducts

Management:

- Surgical resection
- Bismuth Corrlete Type 4 surgical resection is impossible – palliative PTBD

Indications for PTBD in cholangiocarcinoma

In resectable tumors

- Rarely indicated
- Done prior to elective surgery in patients with elevated serum bilirubin

In tumors with borderline resectability

- PTBD with internal to external drainage
- No biliary stenting
- Reduces bilirubin values and chemotherapy can be initiated

In unresectable tumors

- Palliative PTBD
- Alleviate the symptoms of obstructive jaundice
- To reduce serum bilirubin

Goal of PTBD

- Drainage of adequate liver volume
- Resulting in alleviation of symptoms of cholangitis, pruritis
- Reduction of serum bilirubin

What needs to be drained

- 30 % of normal liver parenchyma, 40-50 % of CLD/cirrhotic liver
- Infected undrained segment

Avoid draining

- Atrophic parenchyma
- Lobe with no / restricted portal venous drainage (thrombus / encasement)
- Extensive parenchymal infiltration by tumor

Conclusion

- Palliative PTBD was able to produce a drastic drop in serum bilirubin values
- It also relieved the patient of symptoms of obstructive jaundice

PTBD is the recommended standard of palliative care for cases of obstructive jaundice as it improves the quality of life.

Further read

1. **https://www.ncbi.nlm.nih.gov/books/NBK482302/**
2. **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9273057/**