32 Y Female Patient with Advanced HIV and Diarrhea

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HISTORY

Mrs AL, 32 yr – Female from Rajasthan k/c/o retro viral disease taking irregular treatment P/W

- Weight loss of 15 kgs - 1 year
- Oral ulcers and difficulty in swallowing - 1 month
- High grade fever with chills – 14 days
- Diarrhea (6-7 times ,watery, greenish yellow) -14 days
- Abdominal pain in right hypochondrium -14 days
- Vomiting after food intake- 14 days
- Nausea

No blood in stools, skin lesion, joint pain, yellow urine sclera, abdominal distention

PAST HISTORY

- HIV Reactive since 2010
- Taken ZLN & TDF/FTC/ATV/r from ART center Udaipur
- First ID OPD consult – feb 2016
- Feb 2016 CD4 count: 11 cells/cmm, Presenting illness-PCP pneumonia, TDF/FTC/LPV/r started
- IRIS CMV colitis and cholangitis – April 2016
- Abdominal tuberculosis in April 2016, AKT taken for 9 months
- Took irregular ART and stopped treatment frequently
- Restarted TDF (Tenofovir disoproxil fumarate) +FTC (emtricitabine) + DTG (dolutegravir) + DRV/r(darunavir-ritonavir) before 7 days of current presentation, CD4: 29/cmm

Date	CD4	PVL	ART regimen
2010			ZLN
2012			TDF/FTC/ATV/r
Feb 2016	11		TDF/FTC/LPV/r
June 2016	92	25,60,000	DAR/R/RAL/3TC
July 2016		332	RAL/3TC/DRV/r
Dec 2016	111	37,400	
March 2017		23,300	
June 2017	131	6940	
Nov 2017		4,81,000	TDF/FTC/DTG/DRV/r
Dec 2019	29		TDF/FTC/DTG/DRV/r

PHYSICAL EXAMINATION

- Pallor +
- Oral thrush +
- Cachexia +
- Temperature- Normal
- Pulse- 114/min
- BP- 94/62 mmHg
- RS ,CVS and CNS: unremarkable
- PA- tenderness in right hypochondrium & epigastric region, liver +

SHORT SUMMARY

- A 32 year old female patient, HIV reactive since 2010
- ART defaulter (multiple regimens)
- Low CD4 currently [29 cells/cmm (3%)]
- Presented with small bowel diarrhoea, abdominal pain with prominent upper GI symptoms and fever

RECENT INVESTIGATIONS

- Hb- **8.5gm%**
- WBC- 4800/cumm
- DC- 80/16/1/3/0
- Platelet count- 1,27,000/cumm
- **ESR- 57 mm**
- Na^+- 135 mEq/L
- K^+- 3.75 mEq/L
- S.Creatinine- 0.7 mg/dl
- SPGT-33.29 iu/l
- Bilirubin- 0.24 mg/dl
- ALP -152 (40-104)
- RBS- 109 mg/dl
- CXR(PA)- NAD
- CD4: 29/cmm
- USG abdomen – Dilated CBD, mildly echogenic small bowel mesentry

HOSPITAL COURSE

- ART was continued
- Tab Nitazoxanide 500 mg BID
- Tab Bactrim DS was given 1 BID
- Tab Fole (200) 1 OD
- Supportive treatment

Patient had fever 101.6 F after admission. Blood Culture was sent.

- Inj Ceftrioxone 2gm IV OD was started empirically.
- She remained afebrile after that.

HOSPITAL COURSE

- Patient did not show any improvement in GI symptoms after 2 days of treatment.
- CMV viral load was sent on day 3
- Stool for larvae sent
- Tab Ivermectin 9 mg HS was added for 2 days
- Next day she had marked improvement in nausea and vomiting. Stool frequency decreased
- Blood culture showed growth of GNB after 56 hours of incubation
- Same treatment was continued.

INVESTIGATIONS

- Stool R/M – No pus cells
- Stool – weak ZN stain – Few oocysts of cryptosporidia seen
- Stool for larvae- Negative
- CMV viral load – Not detected
- Blood culture showed **SHIEGELLA** Group resistant to Ceftrioxone
- Identification by MALDI TOF performed **– E. COLI** identified

- Patient responded to the treatment. Abdominal pain decreased, diarrhoea resolved. Patient became afebrile and tolerated food well without nausea and vomiting
- Discharged with ART & Nitazoxanide on 7^{th} day

FINAL DIAGNOSIS

- Small bowel infective diarrhoea (likely strongyloides) with E.Coli bacteraemia, Anaemia and Oral Candidiasis in a patient with advanced HIV infection

CAUSES OF INFECTIOUS DIARRHEA IN AN HIV-INFECTED PATIENT

- Viral
  - *Cytomegalovirus* (CMV)
  - Adenovirus
  - Herpes simplex virus (HSV)
- Parasites
  - *Cryptosporidium parvum*
  - *Giardia lamblia*
  - *Entamoeba histolytica*
  - *Isospora belli*
  - *Cyclospora cayetanensis*
  - *Strongyloides*
  - Microsporidium
    - *Enterocytozoon bieneusi*
    - *Encephalitozoon intestinalis*
- Bacterial
  - *Salmonella* sp
  - *Shigella* sp
  - *Campylobacter jejuni*
  - *Clostridium difficile*
  - *Yersinia enterocolitica*
  - *Escherichia coli*
- Mycobacterial
  - *Mycobacterium avium-intracellulare/complex (MAI/MAC)*
  - *Mycobacterium bovis*
  - *Mycobacterium tuberculosis*

STRONGYLOIDIASIS

- Caused by infection with the helminth *Strongyloides stercoralis* (more prevalent) and *Strongyloides fülleborni* (restricted to certain regions of Africa)
- 30–100 million persons are estimated to be infected worldwide.
- Endemic in rural areas of tropical and subtropical regions, occurs sporadically in temperate areas such as North America, southern Europe, Japan, and Australia.
- Most infections are asymptomatic
- Transmission:
  - Most common mode: filariform larva penetrate skin while contact with contaminated soil
  - Less common modes:
    - faecal-oral transmission and person-to-person transmission (via contact with faecal contaminated fomites).
    - Organ transplant recipient

RISK FACTORS FOR SEVERE DISEASE

- Conditions:
  - Human T-lymphotropic virus type I (HTLV-I) infection
  - HIV/AIDS
  - Malignancy
  - Hypogammaglobulinemia (including nephrotic syndrome and multiple myeloma)
  - Congenital immunodeficiency
  - Alcoholism and/or malnutrition
- Medical interventions:
  - Use of corticosteroids, cytotoxic agents and TNF inhibitors
  - Solid organ transplantation, transmission as well as immunosuppression
  - Hematopoietic stem cell transplantation

CLINICAL SYNDROMES

- Acute strongyloidiasis:
  - Clinical manifestations reflect the path of larval migration from the site of skin penetration to the small intestine
  - Immediate: Irritation at the site of penetration followed by edema or urticaria which may last for weeks.
  - Within a week: Dry cough occurs as larva migrate through the lung and trachea
  - Gastro-intestinal symptoms e.g. diarrhoea, constipation, abdominal pain, vomiting or anorexia may occur as early as 3 weeks after transmission

CLINICAL SYNDROMES

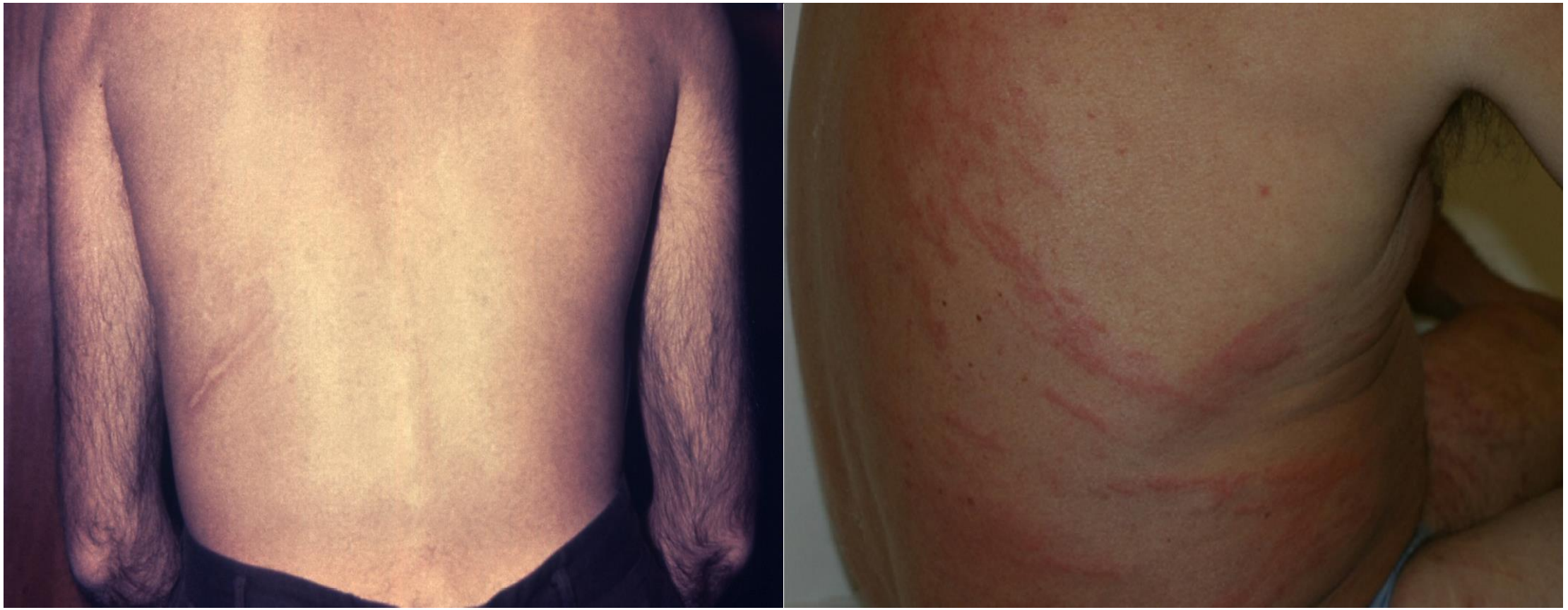
- Chronic strongyloidiasis:
  - Frequently asymptomatic or mildly symptomatic
  - **GI symptoms**: diarrhea, constipation, intermittent vomiting, and borborygmi
  - **Dermatologic manifestations**: larva currens, pruritus, urticaria, and angioedema
  - **Respiratory symptoms**: dry cough, throat irritation, dyspnea, and wheezing (may worsen paradoxically with corticosteroid use)
  - **Unusual symptoms**: nephrotic syndrome, GI bleeding, ascites, chronic malabsorption, hepatic lesions, arthritis, and asthma

CLINICAL SYNDROMES

- Hyper-infection syndrome:
  - Refers to accelerated autoinfection
  - Signs and symptoms are attributable to increased larval migration **within the organs normally involved in the autoinfection cycle** i.e, the GI tract, lungs, and skin
- Disseminated disease:
  - Hyper-infection syndrome with spread of larvae to **organs and tissues outside those in the autoinfection cycle.**

- **Severe manifestations:**
  - **GI symptoms:** abdominal pain (crampy or bloating in nature), watery diarrhea, constipation, anorexia, weight loss, difficulty swallowing, nausea, and vomiting. Bleeding, ulceration, and small bowel obstruction may occur
  - **Respiratory symptoms :** fever, dyspnea, cough, wheezing, choking, hoarseness, chest pain, hemoptysis, and palpitations
    - Chest radiographic imaging may demonstrate bilateral or focal interstitial infiltrates reflecting alveolar hemorrhage
  - **Central Nervous System Manifestations:** Aseptic meningitis or GNB meningitis.
  - **GNB Bacteraemia:** Migration of filariform larvae during autoinfection may facilitate entry of enteric organisms into the systemic circulation.
    - E.coli most common. Others- Proteus mirabilis, Klebsiella pneumoniae, Enterococcus faecalis, and Streptococcus bovis
    - Presentation- bacteraemia, pneumonia, meningitis, sepsis

- **Larva currens:** raised, pink, pruritic, evanescent streaks along the lower trunk, thighs, and buttocks, resulting from migrating larvae through the subcutaneous tissues. Progress 5-15 cm/hour



DIAGNOSIS

- Stool examinations:
  - Direct microscopy: **Rhabditiform larva** can be seen. Sensitivity very low (<50%).
  - Other methods: agar plate culture, sedimentation concentration, Baermann concentration technique
  - Nucleic acid amplification tests (NAATs): greater specificity for diagnosis of Strongyloides than direct stool examination. Availability limited.
- Serologic testing:
  - More sensitive but less specific
  - ELISA, indirect immunofluorescence, immunoblot
  - Limitations: Cross reactivity, unable to differentiate between current or prior infection, decreased sensitivity in HTVL-1 infection and hematological malignancy, and lack of standardization
- Endoscopic findings:
  - Duodenum – Edema, brown mucosal discoloration, erythematous spots, subepithelial hemorrhages, and megaduodenum. Biopsy may demonstrate parasites in the gastric crypts or duodenal glands and eosinophilic infiltration of the lamina propria
  - Colon – Edema, loss of vascular pattern, aphthous ulcers, erosions, serpiginous ulcerations, and xanthoma-like lesions . *Strongyloides* colitis may mimic ulcerative colitis
  - Stomach – Thickened folds and mucosal erosions

TREATMENT

- Treatment with anthelminthic therapy is warranted for symptomatic and asymptomatic individuals, regardless of immune status.

- First line therapy
- **Ivermectin**, 200 µg/kg orally for 2 days

- Relative **contraindications** include the following:
- Confirmed or suspected concomitant *Loa loa* infection
- Persons weighing less than 15kg
- Pregnant or lactating women

- Alternative

- **Albendazole** 400 mg orally two times a day for 7 days.
- Relative contraindications:
- Hypersensitivity to benzimidazole compounds or any component of product
- Use should be avoided in the 1st trimester of pregnancy
- In patients with positive stool examination for *Strongyloides* and persistent symptoms, follow-up stool exams should be performed 2—4 weeks after treatment to confirm clearance of infection. If recrudescence of larvae is observed, retreatment is indicated.

HYPERINFECTION SYNDROME/ SEVERE DISEASE

- Ivermectin (200 mcg/kg per day)
- Empiric antibiotic therapy with activity against enteric gram-negative bacteria.
- In patients on immunosuppressive agents should have these regimens reduced, if feasible.
- The optimal duration of treatment - At least two weeks or until symptoms have resolved and daily stool examination is negative for at least two weeks (one autoinfection cycle)

  - longer duration of treatment may be warranted for patients with persistent immunosuppression.

- Immunocompromised patients require prolonged therapy until sputum and/or stool are negative for 2 weeks. Sometimes repeated courses of treatment are needed.
- In severely ill patients who are unable to take oral drugs, rectal preparations of ivermectin or the veterinary subcutaneous formulation of ivermectin has been used.

- The efficacy of ivermectin (200 mcg/kg per day for one or two days) has been shown to be greater than that of albendazole (400 mg twice a day for three to seven days)