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A CASE REPORT ON CRYPTOCOCCAL MENINGITIS

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ABSTRACT

Cryptococcal Meningitis is an infectious disease of worldwide distribution caused by the fungus Cryptococcus neoformans. The fungus primarily attacks the lungs, causing torulomas, but produces few or no symptoms referable to lungs. Cryptococcal meningitis has become the leading cause of morbidity and mortality from infection in AIDS patients. Approximately 1 million cases of cryptococcal meningitis are reported each year. A 40-year-old female patient was admitted with chief complaints of fever for 15 days which is on and off type associated with headache for 15 days associated with blurring of vision, 10 episodes of vomiting in the past 1 day bilious in nature. Her history says she has been IDV-positive for 2 years on medication. The patients CSF analysis shows the presence of cryptococci micro-organism. And CT shows DNS towards the right side &Mucosal thickening in the bilateral maxillary sinus. The patient was given Inj.Dexamethasone, Inj.Cefotaxime, Inj.Liposomal Amphotericin B, Tab.Fluconazole, Tab.Nitrofurantoin, Syp.Sucralfate, Inj.Metoclopramide, Syp.Potasium chloride, Tab.Cotrimoxazole. As there was a Adverse drug reaction of Amphotericin B induced hypokalemia, Further Investigations are necessary to avoid Drug interactions or ADRs due to ART & treatment of Meningitis.

KEYWORDS: Meningitis, HIV, Opportunistic infections, CT brain, CSF Analysis.

INTRODUCTION

Many microorganisms can cause chronic meningitis. Although tuberculous meningitis is the most common form, especially with the emergence of the acquired immunodeficiency syndrome pandemic, there is an increasing number of cases of fungal meningitis, especially

due to cryptococcal infection, recognized in clinical practice. Cryptococcal meningitis has become the leading cause of morbidity and mortality from infection in AIDS patients.[1]

Cryptococcosis is a major opportunistic infection that causes more than,100,000 HIV-related deaths each year. It was named Busse-Buschke disease due to its first description by Otto Busse and Abraham Buschke in 1894.[2]

Among human immunodeficiency virus (HIV) seropositive individuals, cryptococcal meningitis is the second most common cause of opportunistic neuro-infections and usually occurs in advanced stages. progression of HIV disease. Cryptococcal meningitis is one of the AIDS-defining diseases.[1]

Current trends are changing due to the marked improvement in quality and survival through highly active antiretroviral therapy (HAART). The introduction of the original HAART in India increased the number of people being treated for HIV as the cost of highly active antiretroviral therapy (HAART) was reduced by 20 times.[1] Most HIV-negative cases include patients on immunosuppressive therapy or with organ failure syndromes, transplants, innate immune problems, common variable immunodeficiency syndrome, and congenital immunodeficiency syndrome, haematological disorders.[2]

EPIDEMIOLOGY

Approximately 1 million cases of cryptococcal meningitis are reported each year. Incidence has increased markedly since the 1950s due to the use of corticosteroids and improved survival of cancer patients. However, most reports of cryptococcus date back to the 1980s and are mainly AIDS-related cases. Approximately 6% of AIDS patients have cryptococcal infection, and AIDS-associated cryptococcal infections account for 85% of all patients diagnosed with cryptococcal disease.[2]

C.Gattii is traditionally associated with illness immunocompetent people from tropical and subtropical areas, such as Thailand, northern Australia, New Zealand, and Papua New Guinea, have historically been sickened by C. Gattii. Four C. gattii molecular subtypes have been discovered more recently, and each has unique epidemiological traits that cast doubt on this viewpoint. While VGI (var gattii I) is the predominant subtype in Australasia, immunocompetent patients from British Columbia, Canada, have been reported with an outbreak of sickness that can be linked to VGII. On Vancouver Island, 218 cases were

discovered between 1999 and 2010. After another instance on Orcas Island in Washington, USA, in 2006, C. Gattii became endemic throughout the U.S. Pacific Northwest. There have also been reports of sporadic sickness in other regions of North America, including Florida, North Carolina, Rhode Island, Georgia, New Mexico, Michigan, and Montana. Additionally, patients with HIV infection are more likely than immunocompetent patients to have C. gattii subtypes VGIII and -IV. In some regions of Central and South America and southern Africa, these strains may be responsible for 2.4%–30% of HIV-associated cryptococcosis. Given that many laboratories do not carry out in-depth cryptococcal speciation, the incidence of human disease caused by C. Gattii is likely underreported. Uncertainty exists regarding C. Gattii's environmental reservoirs. It has been isolated in eucalyptus trees in Australia, India, and other Asian nations.38 It has been cut off from non-Eucalyptus tree species, soil, freshwater, and saltwater in British Columbia. This organism's discovery in diverse bio geo climatic zones suggests that either its distribution is growing or that its ecology was previously underappreciated. Climate change and altered land-use practices, like as logging, are two causes of a shifting distribution.[3]

ETIOLOGY

Cryptococcal meningitis is the most common form of fungal meningitis and is caused by Cryptococcus neoformans. C. neoformans is an enveloped hetero basidiomycete fungus.[1] C. neoformans is an environmental saprophyte. The rarity of it being isolated as person-to-person and person-to-person transmission suggests that human infection is a random eventual event in its life cycle. C. neoformans was found as a budding yeast. Yeasts are spherical to oval cells, 5-10 μm in diameter, with the polysaccharide envelope as the major virulence factor and substrate detected by the cryptococcal antigen assay.[4]

Traditionally. C.neoformans is classified into two genera and five serotypes (A, B, C, D, AD) based on its shell structure. C. neoformans var. neoformans includes strains with serotypes A, D, and AD, while. C. neoformans.Var Gurbi includes serotypes B and C. Recent analyses of the URA5 gene and DNA trace models have shown that serotypes A and D have significant genetic differences. Therefore, C. neoformans var. neoformans serotype A has been recognized as a new and named variety. C. neoformans var. Clumsy. Hybrids of serotypes A, D, and AD are globally responsible for 98% of all cryptococcal infections in AIDS patients. Serotypes B and C mainly affect immunocompetent individuals but have also recently been reported in AIDS patients.[1]

Jain studied 57 strains of cryptococcal isolates clinically from several regions of India, of which 51, one was C. neoformans var. neoformans and 5 were C. neoformans var, gurbi. Weathered pigeon droppings often contain C. neoformans var. neoformans and tree litter of the species Eucalyptus camaldulensis and Eucalyptus terreticornis contain Cryptococcus neoformans var. Clumsy. Guqnani isolated C. neoformans var. gurbi and C. neoformans var. gurbi from the flowers and bark of eucalyptus trees in India. With neoformans var. gurbi has also been isolated from decaying wood inside the trunk cavities of 'Syzygium cumin (Java plum, Indian mulberry) trees from northwest India.[1]

The main factor leading to cryptococcal infection is HIV; however, the predisposing factors for non-HIV patients are Syndrome and Autoantibodies.

• Idiopathic CD4 leukopenia.

• Pulmonary alveolar proteinosis with autoantibodies against granulocyte-macrophage colony-stimulating factors

• Autoantibodies against interferon. Single gene disorder:

• Primary immunodeficiency due to GATA2 mutation.

• Chronic granulomatous disease.

• Recurrent hyper immunoglobin E syndrome

• X-linked CD40L deficiency Polygenic variation

• Fcgamma receptor (FCGR) II polymorphism Comorbidities

• Sacoidosis, autoimmune disease, treatment with steroids.

• Liver disease.

• Conditions for solid organ transplantation.[2]

CLINICAL MANIFESTATIONS [5]

Cryptococcal meningitis is an infection caused by the fungus Cryptococcus after it has spread from the lungs to the brain. Symptoms of cryptococcal meningitis include

- Headache
- Fever
- Neck pain
- Nausea and vomiting
- Vision loss
- Confusion or behaviour changes.
- Altered sensorium.

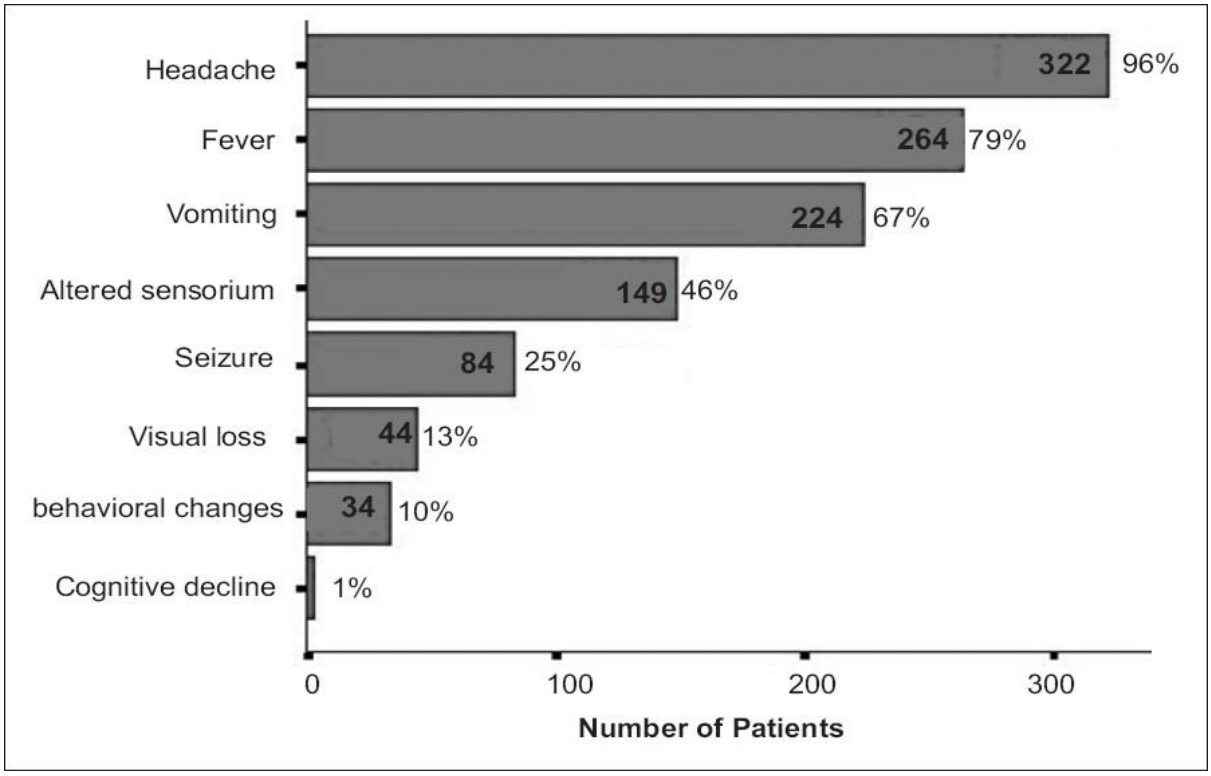

FIGURE [1]

RISK FACTORS [5]

Infection with C. neoformans is rare in healthy individuals. Most C. neoformans infections occur in people with weakened immune systems1-3, such as people who:

• Have severe HIV/AIDS

• Have received an organ transplant, or

• Are you taking corticosteroids, rheumatoid arthritis medications, or other medications that weaken the immune system?

PATHOPHYSIOLOGY

Pathophysiology is determined by the host defence state, the virulence of the cryptococcal strain, and the size of the inoculum. Susceptible hosts are exposed to cryptococci in the environment. The fungus enters the human body by breathing in the lungs.[1]

Once deposited in the pulmonary alveoli, yeast spores must survive at normal levels with high pH and physiological concentrations of carbon dioxide before being phagocytosed by alveolar macrophages, a more acidic environment. and spread after a latent period in the lungs. lymph nodes.[3] This lung infection is usually asymptomatic, but the organism can spread to other organs depending on the individual's immune status. Cerebrospinal fluid is an

ideal site for infection because it lacks complement and immunoglobin. An enzyme called phenol oxidase found in C. neoformans is responsible for the production of melanin. Melanin may act as a virulence factor by rendering organisms resistant to leukocyte attack, reducing lymphocyte proliferation and tumour necrosis factor production.[1] In patients with severe infections, organ dysfunction can rapidly increase, mainly due to tissue deformation due to increasing fungal loads.[3]

DIAGNOSIS

Work on the initial assessment should depend on laboratory tests for CSF. However, to prevent postural herniation, a brain CT MRI scan, or fundus examination should be considered before performing a lumbar puncture.[2]

1. Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain with contrast is performed to exclude focally occupied lesions such as cryptococcal disease and hydrocephalus (Figure 1). Brain scans or magnetic resonance imaging are usually normal but may detect diffuse brain atrophy. The MRI brain mat shows non-contrast dotted spots of CSF density that correlate with the presence of cryptococci in the Virchow-robin space. Sometimes an MRI can even show a pseudocyst.[1]

2.Blood and CSF should be cultured for fungi and tested for cryptococcal antigens. Even with generalized disease, routine laboratory tests may be normal (Figure 2). Open pressure should be measured at the first lumbar puncture, pressure greater than 25 cm of water is a poor prognosis.[2]

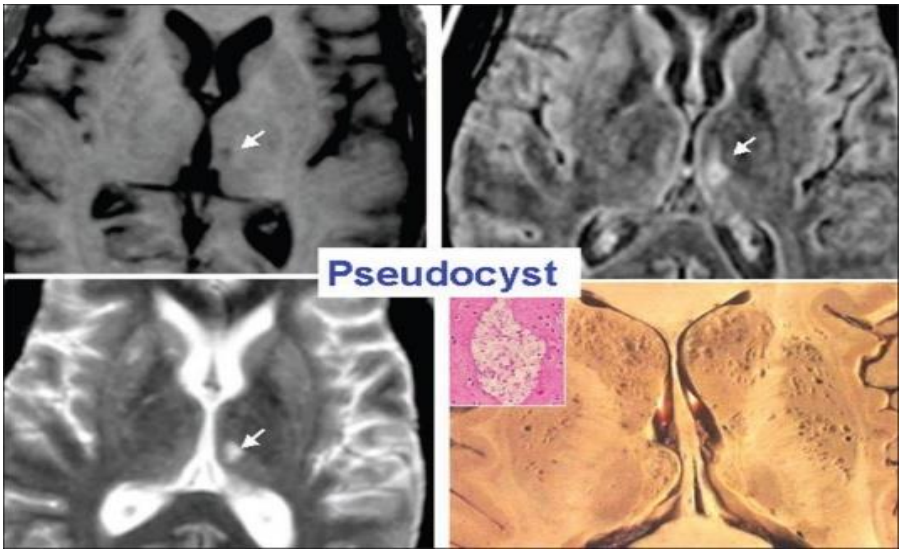

Figure1: Mri Demonstrating Pseudocyst Formation.

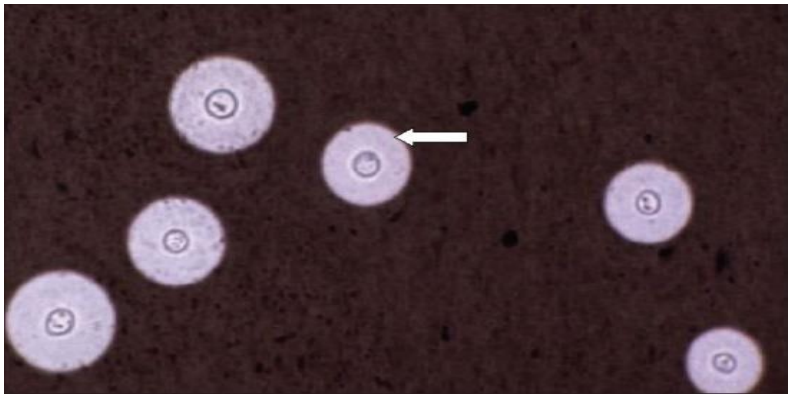

Figure 2: India Ink Stain Showing Capsulated Cryptococci.

COMPLICATIONS[6]

A person can develop complications from cryptococcal meningitis, as well as from the treatment they receive. Complications such as:

• Recurrent cryptococcal infection.

• Epilepsy

• Hearing loss.

• Brain damage.

• Excess fluid in the brain.

TREATMENT[2]

Treatment has remained unchanged for a decade, according to the recommendations of the 2010 update of IDSA (Infectious Diseases Society of America). First-line antifungal therapy is based on induction, reinforcement, and maintenance of the following.

➢ Induction therapy:

- Amphotericin B deoxycholate (0.7-1.0 mg/kg/day) + flucytosine (100 mg/kg/day orally) for 2 weeks.
- Liposome amphotericin B (3-4 mg/kg/day) or amphotericin B lipid complex (5 mg/kg/day; monitor renal function) + flucytosine (100 mg/kg/day) for 2 weeks.
- Amphotericin B deoxycholate (0.7-1.0 mg/kg/day) or liposomal amphotericin B (3-4 mg/kg/day) or amphotericin B lipid complex (5 mg/kg/day, for disease) flucytosine intolerance) for 4-6 weeks.

➢ Induced substitution therapy

- Amphotericin B deoxycholate + fluconazole
- Fluconazole + flucytosine
- Fluconazole

- Itracanzole.

➢ Consolidation treatment

- Fluconazole (400 mg/day) for 8 weeks

➢ Maintenance treatment

- Fluconazole (200 mg/day) for one or more years.

➢ Alternative to maintenance therapy

- Itraconazole (400 mg/day) for one year or more.
- Amphotericin B deoxycholate (1 mg/kg/week) 1 year or more.[2]

➢ Complications of treatment with amphotericin B may include:[6]

- Kidney damage.
- Muscle and joint pain
- Fever, Nausea, and vomiting.

CASE REPORT

A 40-year-old female patient was admitted to Vijayanagara Institute of Medical Science Ballari, Karnataka with chief complaints of fever for 15 days which is onset and off type associated with headache for 15 days associated with blurring of vision, 10 episodes of vomiting for 1 day bilious in nature.

Her history says she has been IDV-positive for 2 years on medication.

On examination, blood pressure BP was found to be 120/80mmHg and pulse rate (PR) 94bpm.

On systemic examination:

Respiratory system: B/L non-vesicular breathing sounds (NVBS) upbeat.

CVS: S1, S2 was positive, no murmur

P/A:Soft non-tender.

CNS: conscious oriented, neck rigidity (+), tone is standard on both sides.

LABORATORY INVESTIGATION

1.HEMATOLOGY				
PARAMETERS	**D1**	**D19**	**D20**	**REFERENCE**
HEMOGLOBIN	11.4	4.3	4.5	12-16 g/dl
RBC	4.31	1.62	1.62	$3.5\text{-}5.0\times10^{6}/mm^{3}$
WBC	7100	6800	7600	4500-11,000cells/cumm
HEMATOCRIT	34	12.8	13.2	33-43%
PlATELETS	2.97	1.47	1.54	1.5-4.5 lacs/cumm

2.ELECTROLYTES	D1	D7	D9	D16	D19	D20	
SODIUM	139	134	144	13	140	142	135-145mEq/L
POTASSIUM	4.2	4.1	4.5	2.1	2.6	4.6	3.5-4.5mEq/L
CHLORIDE	101	102	106	108	109	108	97-107mEq/L

3.RENALFUNCTION TEST	D1	D7	D9	D19	D20	
SERUM CREATININE	0.8	0.9	0.5	1.1	0.7	0.6-1.2 mg/dl
SERUM UREA.	30	22	18	32	34	0-50 g/dl

4.LIVER FUNCTION TEST	D1	D9	
ASPARTATE AMINOTRANSFERASE	32	12	0-35 U/L
ALANINE AMINOTRANSFERASE	12	22	0-35 U/L
ALKALINE PHOSPHATE	83	222	30-120 U/L
TOTAL BILIRUBIN	0.4	1.9	0.1-1 MG/DL
DIRECT BILIRUBIN	0.2	0.6	0-0.2MG/DL
INDIRECT BILIRUBIN	0.2	1.3	0.1-0.8MG/DL

5.CSF ANALYSIS		
PROTEIN	62.8 MG/DL	
SUGAR	49.3 MG/DL	
CELL COUNT	30 CELLS/CUMM	
CELL TYPE	LYMPHOCYTES	
GRAM STAIN & AFB	NEGATIVE	
ALBUMIN	<0.1 G/DL	
ADA	2.0	UPTO 10
I.I.P FOR CRYPTOCOCCI	POSITIVE	

6.CT PNS (PLAIN STUDY)
IMPRESSION: *DNS towards the right side. *Mucosal thickening in the bilateral maxillary sinus.

7.CD4 &CD8		REFERENCE
CD 45 absolute (Lymphocyte Gated)	394	1115-4009/c.mm
CD 3(T Cells) Percentage	77.71	55-81 %
CD 3(T Cells) Absolute	306	457-3926 cells/µL
CD 4(Helper T Cells) percentage	13.54	27-51%
CD 4(Helper T Cells) Absolute	53	448-1611 cells/µL
CD 8(Suppressor T Cells) Percentage	63.42	20.06-42.52%
CD 8(Suppressor T Cells) Absolute	250	218-1396 cells/µL
CD 4/CD 8 RATIO	0.21	0.39-3.02

TREATMENT

DURING the 40 days of stay at the hospital the patient was treated with the following drugs.

SL. NO	DRUGS GIVEN	DOSE	ROUTE	FREQUENCY	NO OF DAYS GIVEN
01	INJ.MANNITOL	100ml	IV	1-1-1	16 DAYS
02	INJ.DEXAMETHASONE	8mg/4mg	IV	STAT/1-0-1	5 DAYS
03	INJ.CEFOTAXIME	2g/1g	IV	STAT/1-0-1	6 DAYS
04	INJ.PANTOPRAZOLE	40mg	IV	1-0-1	21 DAYS
05	TAB.PARACETAMOL	500mg	PO	1-1-1-1	23 DAYS
06	INJ.ONDANSETRON	4mg	IV	1-1-1	21 DAYS
07	IVF(NS)		IV		9 DAYS
08	SYP.SALBUTAMOL	5ml	PO	1-1-1	10 DAYS
09	INJ.LIPOSOMAL AMPHOTERICIN B	150mg in 5D	IV	1-0-0	15 DAYS
10	TAB.FLUCONAZOLE	800mg	IV	1-0-0	20 DAYS
11	INJ.TRAMADOL	100mg in NS	IV	SOS	8 DAYS
12	TAB.NITROFURANTOIN	100mg	PO	1-0-1	2 DAYS
13	TAB.COTRIMOXAZOLE	800/160mg	PO	1-0-0	14 DAYS
14	INJ.METOCLOPRAMIDE	10mg	IV	1-0-1	5 DAYS
15	INJ.KCL	2amp in 1pint NS	IV	STAT	3 DAYS
16	SYP.SUCRALFATE	5ml	PO	1-1-1	5 DAYS
17	SYP.KCL	15ml	PO	1-1-1	3 DAYS
18	TAB.DOMPERIDONE		PO	1-0-1	3 DAYS

DISCHARGE MEDICATION

SL. NO	DRUGS GIVEN	DOSE	ROUTE	FREQUENCY
01	TAB. FLUCANAZOLE	800mg	PO	1-0-0
02	TAB. IFA	333mg	PO	1-0-0
03	TAB. VITAMIN B-COMPLEX	100mg	PO	0-1-0
04	TAB. SEPTRAN DS	800/160mg	PO	1-0-0

CLINICAL PHARMACIST INTERVENTION

- ADR – AMPHOTERICIN B INDUCED HYPOKALEMIA [31.4% to 51.1%].

Reference: Micromedex drug reference.

- Contraindicated drugs have been prescribed:

a) DOMPERIDONE+ FLUCONAZOLE

b) FLUCONAZOLE+ ONDANSETRON

These drugs results in an increased risk of QT interval prolongation.

Reference: Micromedex drug interactions.

DISCUSSION

CRYPTOCOCCAL MENINGITIS Was Named busse-buschke disease due to its first description by Otto Busse and Abraham Buschke in 1894. Among human immunodeficiency virus (HIV) seropositive individuals, cryptococcal meningitis is the second most common cause of opportunistic neuro infections and usually occurs in advanced stages. Cryptococcal Meningitis is the most common form of fungal meningitis after it has spread from the lungs to the brain. It is caused by Cryptococcus neoformans and an environment saprophyte. Based on its shell structure, C. neoformans is classified into two genera and five serotypes (A, B, C, D, AD). Approximately 6% of AIDS patients have this disease and AIDS-associated cryptococcal infections account for 85% of all patients diagnosed with cryptococcal disease. Symptoms include headache, fever, neck pain, vision loss, confusion or behavioral changes, nausea and vomiting. Here is a patient of a forty-year-old female who was admitted to the Department of general medicine female medical ward, unit E with complaints of fever, headache for 15 days, and vomiting for one day, the history of the patient shows that she is IDV (immunodeficiency virus) positive since 2 years on ART (Anti-Retro Viral Therapy) medication. So, the physician had advised to test for CBC, ELECTROLYTES, RFT. The hemoglobin levels were too low indicating life-threatening anemia. I.I.P(idiopathic interstitial pneumonia) test for cryptococcus confirmed positive, CT SCAN OF BRAIN, X-RAY CHEST PA VIEW, CT PNS (PLAIN STUDY) report showed that cryptococcal meningitis with lateral rectus palsy and CT orbit findings showed. Mucosal thickening with bubbly lucencies is seen in bilateral sphenoid sinuses. Mild mucosal thickening was seen in bilateral ethmoid sinusitis. Reduced CD3 and CD4 cells. Based on the laboratory reports the diagnosis was confirmed as CRYPTOCOCCAL MENINGITIS. The main treatment for cryptococcal meningitis was Inj. liposomal amphotericin B 150mg (1-0-0), tab. flucytosine 100mg (1-1-1) along with the ART regimen. Cryptococcal Meningitis.

CONCLUSION

Cryptococcal meningitis is the second most common cause of opportunistic neuro infections and usually occurs in advanced stages. It is caused by Cryptococcus neoformans and an environment saprophyte. In this patient the Physicians have followed the standard treatment of Cryptococcal Meningitis. Along with the ART treatment the patient should adhere to the medication of Meningitis. As there was a Adverse drug reaction of Amphotericin B induced hypokalemia, the should report any further abnormalities to the physicians. As both the

treatment of ART and Meningitis can cause many ADRs. Further Investigations are necessary to avoid Drug interactions or ADRs due to ART & treatment of Meningitis.

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