Case Report

A Rare Case Report-Idiopathic CD4 Lymphocytopenia Leading to Disseminated Histoplasmosis

Shivangi Tiwari, S.B Gawarikar, Ashish Sharma, Tabraiz, Ambika Sen Gupta, Pulkit Jain

Histoplasmosis, a granulomatous mycosis caused by the intracellular dimorphic fungus *Histoplasma capsulatum*, has not been reported in Indian literature. The clinical spectrum of histoplasmosis varies from asymptomatic infections to disseminated histoplasmosis (PDH), depending on the intensity of the injury and the immunity of the exposed person. Infections most often occur in immunocompromised individuals, especially those with compromised immune systems such as HIV with low CD4+ lymphocytes, malignancies, or those who have received other immunosuppressive therapies. Keeping a high clinical suspicion regarding a differential diagnosis of histoplasmosis is required to prevent misdiagnosis, particularly in high-risk patients and initiate early antifungal therapy, which ameliorates the patient's prognosis. Here, we present a case report of a middle-aged diabetic man who presented in our institute as a referral case from a private hospital with complaints of anorexia, fatigue, low-grade fever and decreased urination for 2 months with subsequent weight loss. His bone marrow biopsy confirmed infiltration with *H. capsulatum*. Subsequent 6 week apart CD4 counts were less than 300/mm^3 without HIV-positive status or other acquired immunodeficiency, consistent with idiopathic cd4 lymphocytopenia. After a varied clinical course of intensive care stay, the patient was well treated with antifungal medications, showed remarkable improvement and was subsequently discharged in good condition.

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Keywords: Histoplasmosis, Idiopathic CD4 Lymphocytopenia, Disseminated, Immunodeficiency.

Introduction

Histoplasma capsulatum, a thermally dimorphic fungus, is the etiologic agent of histoplasmosis. Mycelia—the naturally infectious form of *Histoplasma* have a characteristic appearance, with microconidial and macroconidial forms. Shortly after infecting the host, mycelia transform into the yeasts that are found inside macrophages and other phagocytes. The yeast forms are characteristically small (2–5 μm), with occasional narrow budding, Figure 1.[1-3] Activities associated with high-level exposure include excavation, cleaning of chicken coops, demolition and remodeling of old buildings, and cutting of dead trees. It is primarily a pulmonary disease but can progress to disseminated disease in immunocompromised patients.[3] In our patient's subsequent 6 weeks apart, CD4 counts were less than 300/mm^3 without HIV positive status or other acquired immunodeficiency, consistent with idiopathic CD4 lymphocytopenia,[4] which led to such dissemination, which was finally diagnosed only after bone marrow examination.

Case report

A 45 year old male working at a grain house was referred from a private hospital where he was admitted in view of decreased appetite, generalized fatigue, low-grade fever and reduced urine output since the past 2 months, with co-morbidities type 2 diabetes mellitus and systemic HTN since 10 years, on regular medications. He was diagnosed with right-eye ischemic optic neuropathy 3 years back.

On general examination, the patient was found to be cachexia and febrile. The pulse was 104 per minute, Blood pressure was 100/70 mm of hg in right upper arm- supine position and the respiratory rate was 32 per minute with a tracheostomy tube in situ on SIMV mode of ventilation, Fio 2 to 70%. Pallor- present, no lymphadenopathy.

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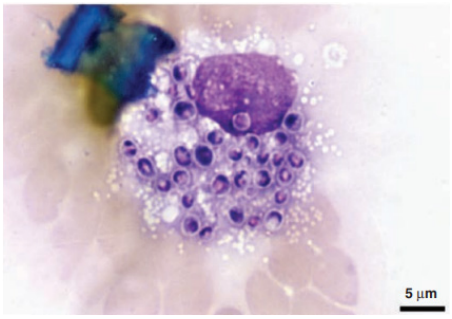

Figure 1: Intracellular yeasts of *H. capsulatum* within an alveolar macrophage

Systemic examination revealed- the liver was enlarged, firm, tender, and 6 cm below the right coastal margin. The spleen was also palpable, firm, nontender and 4 cm below the left coastal margin. Respiratory system -coarse crepitations in the bilateral interscapular and infrascapular region.

Routine investigations revealed anemia, thrombocytopenia, an increased alkaline phosphatase level, raised inflammatory markers and negative viral markers like HIV/Hbsag/HCV (Table 1).

Chest x-ray- suggestive of bilateral ground glass haziness with obscured right CP angle.

USG whole abdomen showed Mild to moderate hepatomegaly with moderate splenomegaly.

CECT chest

- Diffuse B/L ground glass haziness with mild septal thickening.
- Right-sided mild pleural effusion.
- Few sub-centimeter-sized mediastinal lymph nodes.

CECT abdomen

- Moderate hepatomegaly with marked splenomegaly and splenic infarct.
- Moderate ascites.
- Few enlarged lymph nodes along the celiac axis/ hepatic artery.

Bone marrow aspiration

smear shows oval budding yeast-like parasite in macrophages resembling *Histoplasma*

Bone marrow biopsy

increased histiocytes with intracellular capsulated organism morphologically consistent with *H. capsulatum* s/o histoplasmosis.

After the final diagnosis, the patient was managed with liposomal amphotericin B 3 to 5 mg /kg/day for 1 week (ideally, it should have been 2 weeks), which was stopped in view of rapidly declining renal function, serum creatinine reaching value of 5.1, the patient was continued on oral itraconazole 200 mg BD. Apart from this he was managed with higher antibiotics based on susceptibility testing, injection human albumin, various blood products, other symptomatic management, nutritional support and physiotherapy.

Patient showed remarkable improvement after antifungal medications were started, was weaned off from the ventilator, the tracheostomy tube removed and regained speech fluency after a few days. He was discharged successfully on oral itraconazole 200 mg BD to be continued for 1 year and advised monitoring of liver and renal function tests.

Discussion

Considering this case report, since disseminated histoplasmosis is not a commonly encountered entity before coming to our hospital, during an initial patient presentation, a diagnosis of pancytopenia with hepatosplenomegaly was made at a private facility where the patient was admitted firsthand, and all the relevant investigations were done, some specific tests were also performed to rule out common infectious conditions, including pulmonary tuberculosis, immunodeficient conditions like HIV-AIDS. The patient showed no clinical improvement with empirical treatment and supportive care, and the patient's condition kept deteriorating further.

Then he again switched to another private hospital where, in view of his dull and drowsy condition along with severe respiratory distress, he was intubated and taken on mechanical mode of ventilation, and in view of prolonged respiratory support, he was tracheostomized, higher antibiotics were started based

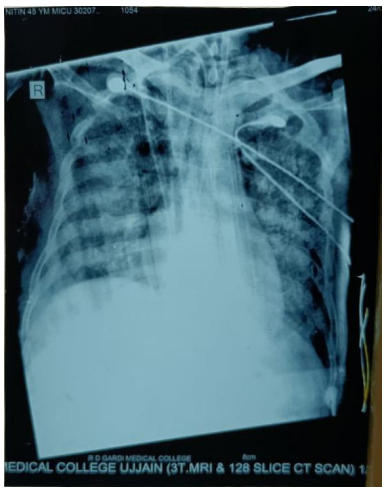

Figure 2: Chest x-ray

Table 1: Investigations

Cbc	Hb	6.8 g/dl
	Rbc	2.50[10^6/uL]
	Wbc	3.2[10^3/uL]
	Platelet	26[10^3/uL]
	Esr	12 mm in one hour
Renal function test	Urea	78.1 mg/dl
	Creatinine	3.5 mg/dl
Liver function test	Total bilirubin	1.3 mg/dl
	Albumin	3.0 g/dl
	Sgot	34.9 U/L
	Sgpt	20.4 U/L
	Alp	662 U/L
Serum electrolytes	Sodium	126.5 mmol/l
	Potassium	3.7 mmol/l
Urine analysis	Pus cells	46
	Sugar	Present
Retic count		4%
Hba1c		5.5%
CD4 COUNT		159
(6weeks apart)		198
CRP		48.8
HIV 1 and 2	Non-reactive	
HbsAg	Non-reactive	
Malaria antigen	Negative	
Typhidot-IgG,IgM	Negative	
Dengue –	Negative	
Ns1 antigen	Negative	
IgG, IgM		
Procalcitonin	0.72 (at admission)	
	0.06 (at discharge)	

on culture sensitivity of blood and sputum, injection human albumin. In view of persistent fever, altered consciousness and since no improvement in clinical condition occurred, a bone marrow examination was performed, which demonstrated the presence of *Histoplasma* in both aspiration and marrow biopsy, which clinched the diagnosis of disseminated histoplasmosis and then relevant antifungal, i.e., liposomal amphotericin B was started. Patient was weaned off from the ventilator and was able to maintain saturation. Still, it had to be withdrawn after 5 days due to rapidly declining renal function, and again patient landed up in respiratory distress and volume overload condition, leading to reintubation.

After such a long and hefty clinical stay patient was discharged from that hospital and then finally referred to C R Gardi Hospital Ujjain, where he was received in a very poor clinical condition with tracheostomy in situ, on the mechanical mode of ventilation and infusion Lasix. Here, he was managed with culture-sensitive antibiotics, antifungal agent Itraconazole, diuretics, prokinetic agents, potassium supplementation, and other supportive measures, along with strict clinical monitoring. Apart from this, he had continuous access to limb and chest physiotherapy and proper nutritional supplementation.

Following this, the patient had drastic clinical improvement as evidenced from his weaning off ventilator support and subsequent removal of tracheostomy tube with suture closure, regaining of voice, all metabolic parameters improved, relief from respiratory distress, regaining of appetite and improvement in overall health status.

The clinical spectrum of histoplasmosis ranges from asymptomatic infection to life-threatening illness, from acute pulmonary then chronic/cavitatory pulmonary to progressive disseminated histoplasmosis.[1,8] Pulmonary involvement is present in up to 90% of cases and the most common chest X-ray finding is prominent bronchovesicular markings as seen in our case.[5] Once inside the body, histoplasma can spread to multiple organ systems, causing a disseminated infection.[7] The clinical presentation of pulmonary and disseminated histoplasmosis can be easily confused with tuberculosis, sarcoidosis, malignancy and other fungal infections (*Aspergillosis, Blastomycosis*).[1] PDH is typically seen in immunocompromised individuals, who account for ~70% of cases. Disseminated infections have an acute, rapidly fatal course leading to diffuse interstitial lung infiltrates and multiorgan dysfunction. Common manifestations include fever, weight loss, hepatosplenomegaly, and thrombocytopenia.

Idiopathic CD4 lymphocytopenia (ICL) is a rare syndrome with absolute CD4 T lymphocyte count <300/μLor < 20% of total T cells on two occasions(6 weeks apart) in the absence of HIV 1 and 2 infection and other immunosuppressive conditions,[4] as evident in our case, moreover we ruled out the common immunocompromised conditions including his immunoglobulins (IgG, IgA, IgM) and complement levels which were within normal limit.[8] HIV 1 and 2 and other viral infections (Hepatitis B, C) that can cause CD 4 cell lymphopenia were also negative. Common diagnostic tests include the detection of *Histoplasma* antigen in BAL fluid or serum, *Histoplasma* serology (IgG and IgM antibodies), and fungal stains of cytopathology or biopsy materials are required in disseminated infections.(6) Antigen levels correlate with the severity of illness in PDH and can be used to follow disease progression, as levels predictably decrease with effective therapy.

Conclusion

Histoplasmosis in not uncommon in India and may well be an under-recognized disease(6). Tests for *Histoplasma* antigen and serology are not commercially available

in India and therefore, the true disease burden could be even higher. The association of histoplasmosis and Idiopathic CD4 Lymphocytopenia is rare.[4]

We suggest that CD4 count should be done in all cases of histoplasmosis, even in HIV-negative individuals to rule out Idiopathic CD4 Lymphocytopenia.[4]

It should invariably be considered in the differential diagnosis if male patients present with prolonged fever, adrenal enlargement, hepato-splenomegaly, oral ulcers and granulomas on HPE.[5,6] Confirmation of the diagnosis requires histopathology, including fungal staining of granulomas and/or culture of appropriate samples.[8] Treatment with itraconazole leads to an excellent outcome in the majority of patient.

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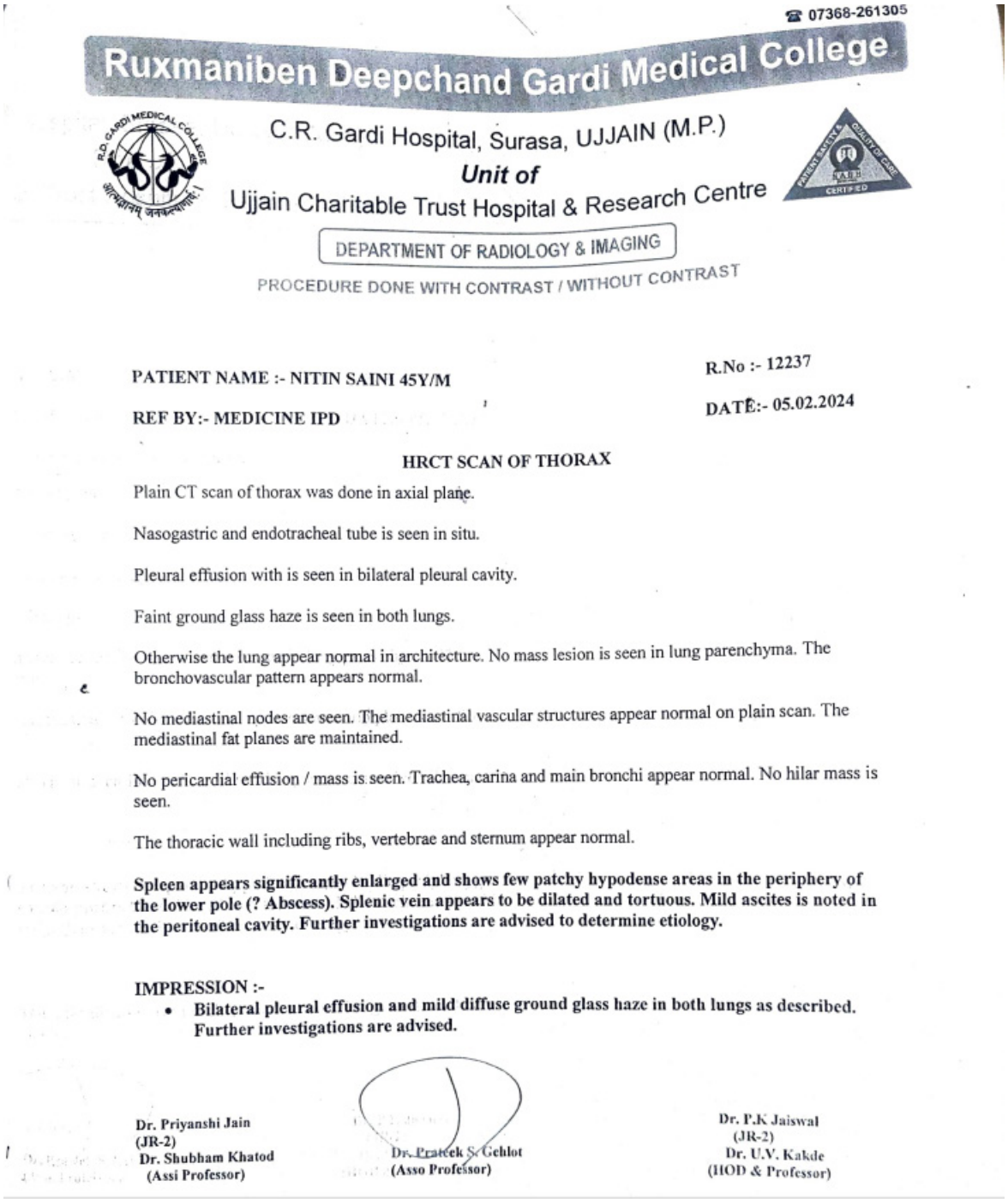
ANNEXURES



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Ruxmaniben Deepchand Gardi Medical College

C.R. Gardi Hospital, Surasa, UJJAIN (M.P.)

Unit of

Ujjain Charitable Trust Hospital & Research Centre

DEPARTMENT OF RADIOLOGY & IMAGING

PROCEDURE DONE WITH CONTRAST / WITHOUT CONTRAST

PATIENT NAME :- NITIN SAINI 45Y/M **R.No :- 12237**

REF BY:- MEDICINE IPD **DATE:- 05.02.2024**

HRCT SCAN OF THORAX

Plain CT scan of thorax was done in axial plane.

Nasogastric and endotracheal tube is seen in situ.

Pleural effusion with is seen in bilateral pleural cavity.

Faint ground glass haze is seen in both lungs.

Otherwise the lung appear normal in architecture. No mass lesion is seen in lung parenchyma. The bronchovascular pattern appears normal.

No mediastinal nodes are seen. The mediastinal vascular structures appear normal on plain scan. The mediastinal fat planes are maintained.

No pericardial effusion / mass is seen. Trachea, carina and main bronchi appear normal. No hilar mass is seen.

The thoracic wall including ribs, vertebrae and sternum appear normal.

Spleen appears significantly enlarged and shows few patchy hypodense areas in the periphery of the lower pole (? Abscess). Splenic vein appears to be dilated and tortuous. Mild ascites is noted in the peritoneal cavity. Further investigations are advised to determine etiology.

IMPRESSION :-

- **Bilateral pleural effusion and mild diffuse ground glass haze in both lungs as described. Further investigations are advised.**

Dr. Priyanshi Jain
(JR-2)
Dr. Shubham Khatod
(Assi Professor)

Dr. Prateek S. Gehlot
(Asso Professor)

Dr. P.K Jaiswal
(JR-2)
Dr. U.V. Kakde
(HOD & Professor)

DEPARTMENT OF IMAGING
SECTION OF MRI / C T SCAN

Patient Name	: Mr. SAINI NITIN BABULAL	IP/OP No	: 2324291	Age	: 45
Refered By	: Dr. Ravi Rathi	Bed No	: 458	Sex	: M
Date	: 16/01/2024	Ref No	: 77042918		
Ward	: 04th Floor				
User ID	: 0620 17/01/2024 3:51:08 PM	Page No	: 1		

HRCT CHEST

Technique: HRCT chest has been performed from thoracic inlet to the level of adrenals and is evaluated with appropriate window settings.

Clinical details: Follow up case of disseminated histoplasmosis with pulmonary edema. Previous CT scan dated 02.01.2024 is available for comparison.

Imaging Findings:

Tracheostomy, Ryle's tube and central line are seen in situ.

As compared with the previous scan, present study reveals -

Marked increase in pulmonary edema with multiple patchy - confluent perihilar ground glass opacities / consolidations seen in present scan.

Marked increase in bilateral pleural effusions with atelectasis of underlying lung segments also noted.

Bony cage and adjacent soft tissue appear unremarkable.

Tracheo-bronchial tree and esophagus appear normal.

No significant mediastinal/axillary lymphadenopathy noted.

Dr. Kiran Chouhan, MD
Consultant Radiologist

Dr. Neeti Mittal, MD
Consultant Radiologist

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SECTION OF MRI / C T SCAN

Patient Name	: Mr. SAINI NITIN BABULAL	IP/OP No	: 2324291	Age	: 45
Refered By	: Dr. Ravi Rathi	Bed No	: 1112	Sex	: M
Date	: 02/01/2024	Ref No	: 77042764		
Ward	: 11th Floor				
User ID	: 0620 03/01/2024 1:31:59 PM	Page No	: 1		

CECT ABDOMEN + CHEST

Technique: A plain and post contrast (oral + IV) CT study of the abdomen and chest has been performed.

Clinical details: Patient presented with decreased appetite / weight loss for 1 month. Fever for 15 days. Left upper quadrant abdominal pain with altered sensorium for 5 days. Patient had pancytopenia with AKI with dyselectrolytemia. Bone biopsy suggestive of histoplasmosis.

Imaging Findings:

CECT abdomen -

Liver is moderately enlarged, measures approximately 17 cm in maximum craniocaudal extent and shows heterogeneous appearance / enhancement. Intrahepatic biliary radicles appear undilated.

Few enlarged lymph nodes are noted along the celiac axis / hepatic artery, the largest one measuring 2.0 x 1.5 cm.

Gall bladder is well distended and does not reveal any radio-opaque calculus or wall thickening.

Spleen is markedly enlarged, measures approx 19.4 in maximum craniocaudal extent and reveals a moderate sized wedge shaped hypoenhancing lesion in its lower body region, measures approximately 5.6 x 2.2 x 1.5 cm - likely splenic infarct.

Adrenals, pancreas and both kidneys appear normal in size and do not reveal any focal lesion.
Urinary bladder is well distended and appears normal.
Small and large bowel loops appear unremarkable.
Abdominal vasculature appears unremarkable.

There is mild ascites with generalised mesenteric fat stranding and subcutaneous oedema.

Visualized bones appear unremarkable.

Patient Name	: Mr. SAINI NITIN BABULAL	IP/OP No	: 2324291	Age	: 45
Refered By	: Dr. Ravi Rathi	Bed No	: 1112	Sex	: M
Date	: 02/01/2024	Ref No	: 77042764		
Ward	: 11th Floor				
User ID	: 0620 03/01/2024 1:31:59 PM	Page No	: 2		

CECT chest -

Diffuse ground-glass haziness with mild septal thickening seen involving both lungs, predominantly in perihilar region with relative sparing of the subpleural region.

Mild centrilobular emphysematous changes are noted involving bilateral upper lobes.

There is mild right pleural effusion with underlying basal atelectasis.

Few centimeter subcentimeter sized mediastinal lymph nodes are noted.

Trachea and main stem bronchi appear normal,
Mediastinal vascular structures are unremarkable.
Trachea and main stem bronchi appear normal.
Visualized bones appear unremarkable.

Impression:

In a k/c/o histoplasmosis, present CT reveals moderate hepatomegaly and marked splenomegaly with likely a splenic infarct along with changes of volume overload and pulmonary edema as described.

Dr. Kiran Chouhan, MD
Consultant Radiologist

Dr. Neeti Mittal, MD
Consultant Radiologist

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DEPARTMENT OF IMAGING
SECTION OF ULTRA - SOUND

Pt Name	Nitin Babulal Saini	45 Y/M	2324291
Ref By	Dr. Ravi Rathi	458	13.01.2024

USG - UPPER ABDOMEN

Suboptimal scan due to bowel gas.

Liver shows mild to moderate enlargement, measures approx 17.1cm. Prominence of periportal echoes, *however no obvious focal lesion seen.* Margins are smooth and regular. The portal vein and biliary radicals are normal in calibre.

GB is distended. ***Sludge seen in lumen. Mild GB wall edema noted.*** CBD is within normal limits.

Pancreas obscured due to bowel gas.

Rt. Kidney : 10.1 x 4.2 cm
Lt. Kidney : 11.4 x 4.0 cm
Bilateral kidneys are normal in size and echotexture. ***Cortical echogenicity is slightly increased****, however corticomedullary differentiation is maintained.* No e/o hydronephrosis or hydroureter.
Bilateral perinephric fat is echogenic. Renal sinus fat is echogenic.

Spleen shows moderate enlargement, measures approx 19.6 x 6.9 cm. A relatively ill defined hypoechoic area of size approx 4.6x 3.2 x 2.8 cm with no internal vascularity seen in mid / lower body region- likely splenic infarct.

Mild ascites seen.
Bilateral pleural effusion (approx volume 900-950 cc on right side & approx volume 300-350 cc on left side) with underlying collapse / consolidation of basal lung.

Bowel loops show normal peristalsis.
Mesentery appears echogenic.

Suggest: Clinical and lab test correlation.

Dr. M Gupta Radiologist | Dr. K Soni Radiologist | Dr. S. [illegible] Radiologist | Dr. P. Shrivastava RMO | Dr. S.Rangwala RMO | Dr. M.Khandelwal RMO | Dr. S.Gupta RMO | Dr. S.Bharuka RMO

Note: All USG finding are dynamic in nature and are subjected to change with course of disease and time, referring clinician are advised to correlate USG findings with clinical findings

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Neuberg Supratech

REFERENCE LABORATORIES

(A unit of Neuberg Diagnostics Private Limited)

LABORATORY REPORT

Name	:Mr. NITIN SAINI	Sex/Age	: Male/ 45 Years	H.ID : 236H03628	Case ID : 31201607178
Ref By	:Dr. Self	Dis.Loc.	:		Pt ID :
Bill. Loc.	:INDORE DIAGNOSTIC SOLUTIONS PVT LTD QUALITY DIAGNOSTICS INDORE				Pt. Loc. :
Registration Date & Time	: 30-Dec-2023 21:33	Sample Type	: Biopsy		Ph # :
Sample Date & Time	: 30-Dec-2023 21:33	Sample Coll. By	:		Ref Id :
Report Date & Time	: 03-Jan-2024 08:47	Acc. Remarks	:		Ref Id2 :

Histopathology Report

Specimen :
Bone marrow trephine biopsy for histopathological examination.

Macroscopic Examination :
Received single elongated pieces of bony tissue measuring 0.5cm in length. Whole processed.
1[HE]

Microscopic Examination :
Sections reveal marrow tissue with normal cellularity. The myeloid precursors show normal distribution & maturation. The erythroid series reveal normoblastic maturation.The megakaryocytes & plasma cells are normal in number and morphology. There is increased histiocytes with intracellular capsulated organism morphologically consistent with histoplasma capsulatum.

Impression :
Histoplasmosis, BM trephine biopsy.
There is no evidence of granulomatous pathology, metastatic deposits or plasma cell proliferative disorder in the examined material.

---------- End Of Report ----------

Grossing By : Dr. Chetana Bora

For test performed on specimens received or collected from non-NSRL locations, it is presumed that the specimen belongs to the patient named or identified as labeled on the container/test request and such verification has been carried out at the point generation of the said specimen by the sender. NSRL will be responsible Only for the analytical part of test carried out. All other responsibility will be of referring Laboratory.

Dr. Soma Yadav
M.D. (Pathology)

Printed On : 03-Jan-2024 08:57

Quality & Diagnostics Imaging

Dr. Ankita Kothari
MBBS, MD, DNB (Pathology)
Ex. SR, TMH, Mumbai
Reg.No. MP-14455

Patient Name	: **Mr. Nitin Saini**	Registered On	: 30-Dec-2023 06:01 PM
Patient ID	: 301223104	Sample Collected On	: 30-Dec-2023 06:01 PM
Age/Gender	: 45 Years / Male	Sample Reported On	: 01-Jan-2024 02:59 PM
Ref. By	: Universal	Sample Type	: BLOOD
Mob No	: 9827505058	Sample ID	

Bone Marrow Aspiration

Test Name	Observed Values
EASE OF ASPIRATION :	Easy
CELLULARITY :	Normocellular
M:E RATIO :	4:1
ERYTHROPOIESIS :	Normoblastic
GRANULOPOIESIS :	Sequential
MEGAKARYOPOIESIS :	Normal
LYMPHOCYTES :	Within Normal Limits.
PLASMA CELLS :	Increased
ABNORMAL CELLS :	Increased macrophage number seen.
PARASITE :	Smear show oval budding yeast like parasite in many macrophages resembling histoplasma.
IMPRESSION :	Bone marrow infiltration by parasite, most likely histoplasma. Kindly correlate with trephine biopsy.

END OF REPORT

Page 1 of 1

Dr. Vinay Bohara
MD,DM Haematology
FBMT Haematologist