

Title: Disseminated Tuberculosis with Testes Involvement: An Intriguing Case Report

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Highlights

- Diagnosing disseminated tuberculosis (TB) is challenging
- Disseminated TB mimics various conditions like infarction, cancer, torsion etc.
- In our case, the patient underwent a myriad of tests before getting a definitive diagnosis

- 1 • This case report highlights the importance of histopathology to diagnose disseminated TB as cytological
2 analysis might miss it
3 • Disseminated TB is relatively rare in immunocompetent adults and might be missed initially and a high
4 level of suspicion is needed
5

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16 **Discussion Points:**

- 17 • What are the typical symptoms and clinical findings associated with disseminated tuberculosis, and how
18 do they differ from other conditions that may mimic it?
19 • How can the diagnosis of disseminated tuberculosis be challenging, especially in cases with atypical
20 presentations such as testicular involvement? What diagnostic tools and tests can be utilized to confirm
21 the diagnosis?
22 • Discuss the significance of histopathological examination, including the identification of tuberculous
23 granulomas with caseating necrosis, in confirming the diagnosis of disseminated tuberculosis. How
24 does it differ from other conditions?
25 • What are the implications of this case report for the management and treatment of disseminated extra-
26 pulmonary tuberculosis with testicular involvement? How important is regular follow-up in monitoring
27 the patient's recovery?
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1 **ABSTRACT.**

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3 **Background:** Disseminated tuberculosis (TB) is the presence of two or more noncontiguous sites resulting from
4 hematogenous dissemination of *Mycobacterium tuberculosis*. We report a case of disseminated TB with
5 testicular involvement.

6 **Case:** A 21-year-old male patient presented to the outpatient department (OPD) with bilateral testicular
7 enlargement and tenderness for last six months. It was suspected to be a case of epididymo-orchitis and
8 empirical antimicrobial therapy was initiated. However, ultrasonography findings were inconsistent with
9 epididymo-orchitis. Two weeks later the patient again presented with increased nodularity in the right testes.
10 Non-seminomatous germ cell tumor was suspected. However, tumor markers came back normal. Magnetic
11 resonance imaging revealed enlarged lymph nodes in the right inguinal and retroperitoneal region raising a
12 suspicion of testicular lymphoma. Positron emission tomography with computed tomography showed multiple
13 lymphadenopathies. Histopathology of the left axillary lymph node finally confirmed the diagnosis to be
14 tuberculosis. No drug resistance were found and the patient responded well to anti-tubercular drugs.

15 **Conclusion:** Diagnosing disseminated TB is difficult as it mimics conditions, such as infarction, cancer, torsion,
16 etc. Attention to small details is necessary. We faced a similar situation in our patient. The patient went through
17 a myriad of tests before finally being diagnosed with TB. Histopathological study was able to get it whereas
18 cytology could not. Similar and totally opposite cases were found in the literature. This highlights the difficulty
19 and importance of these type of cases.

20

21 **Key Words:** Extra-pulmonary Tuberculosis, Lymphoma, Testicular Cancer, Testicular Tumor, Urogenital
22 tuberculosis, Male Genital Tuberculosis (Source: MeSH-NLM).

23

1 **INTRODUCTION.**

2

3 Disseminated tuberculosis (TB) is common in low and middle-income countries and especially among children
4 below 15 years of age. However, its prevalence in developed countries is rising due to various risk factors, such
5 as Human immunodeficiency virus (HIV), immunosuppressive medications, organ transplantation, alcohol
6 consumption, and other comorbidities.¹ Disseminated TB in an immunocompetent adult, comprises <2% of all
7 TB and up to 20% of all extra-pulmonary TB.¹ The true global incidence is likely underestimated due to the
8 challenges in diagnosis.¹ It can involve many organs like lymph nodes, liver, bone marrow, kidney, testis etc.
9 Clinical presentation varies widely in disseminated TB, ranging from subacute or chronic constitutional
10 symptoms like fever, weight loss, and night sweats to multi-organ failure in severe cases.¹ Uncommonly it can
11 present as anorexia and pyrexia of unknown origin.¹ Symptoms in children are quite vague, making the
12 diagnosis quite difficult.¹ It often mimics various conditions like torsion and infarction (painful testicular mass) or
13 cancer (widespread involvement) etc. The key to differentiate between various differential diagnoses is by
14 diagnostic tests like imaging, microbiological tests, tissue biopsy, etc. Mantoux test is often negative in
15 disseminated TB thus not so reliable.¹ Chest radiograph is often the initial imaging modality, showing
16 characteristic miliary patterns in a majority of cases.¹ Other imaging modalities, including high-resolution
17 computed tomography (CT), abdominal ultrasonography, magnetic resonance imaging (MRI), and positron
18 emission tomographic CT (PET-CT), can assist in identifying affected organs and guiding the collection of
19 appropriate specimens for diagnosis.¹ Microscopically there are tuberculous granulomas with or without central
20 caseation. Acid-fast bacilli may be found in epithelioid cells or inside caseation. The nonspecific nature of the
21 symptoms poses a challenge in diagnosing the disease.¹ Here, we describe a rare case of disseminated TB
22 with testicular involvement, mimicking cancer. This case report highlights the critical need for considering
23 tuberculosis as a diagnosis in testicular masses, emphasizing the diagnostic challenges and atypical
24 presentations mimicking other condition(s), and is crucial for timely and accurate management.

25

1 THE CASE

2 Initial Presentation

3 A 21-year-old male presented to the outpatient department (OPD) with complaints of bilateral testicular
4 enlargement for last six months. On examination, both testes were tender, hard and enlarged with loss of
5 testicular sensation as reported by the patient. He was of average built and not had any other complaints. He
6 was not currently on any medications and denied any addictions or sexual contact in his life. He denied any
7 history of pulmonary disease or problem. A provisional diagnosis of bilateral epididymo-orchitis was made and
8 the patient was started on empirical antimicrobial therapy. To confirm the diagnosis, urine was sent for routine
9 examination, microscopic examination, and culture which came out normal. Ultrasonography of the scrotum and
10 testis was also advised.

11 Diagnostic Challenges

12 Follow up visit a week after empiric therapy showed improvement as pain and tenderness reduced. Two weeks
13 later, the patient again presented to the OPD with a new onset nodularity of the right testis with thickening of
14 the spermatic cord which was not present in the previous OPD visit. Based on scrotal edema, clinical findings
15 suggested a suspected non-seminomatous germ cell tumor, clinically categorized as T4 (As per TNM staging
16 system), with invasion of the spermatic cord and pelvic lymphadenopathy.

17
18 However, testicular tumor markers were found to be within the normal limits [LDH - 171U/L (120-246U/L), β -
19 hCG - <0.100mIU/ml (<2.6mIU/ml) and α -fetoprotein - <1.3ng/ml (<8.1ng/ml)]. Later on, MRI of the pelvis and
20 scrotum was done which showed ill-defined T2 hypointensities in both testes along with multiple perifocal
21 satellite hypo-intense lesions. Similar involvement is seen in the epididymis and bilateral spermatic cord (more
22 on the right side). A mild right-sided hydrocele was noted. Also, mildly increased fluid in the left testis was
23 observed. Visible parts of the right ureter were dilated. Enlarged lymph nodes in the right inguinal and
24 retroperitoneal region (mainly the left para-aortic region) were noted. A testicular lymphoma was then suspected
25 based on extensive lymphadenopathy and the absence of any history of tuberculosis.

26
27 ¹⁸F-DG whole-body PET-CT was done to determine spread. It showed metabolically active multiple
28 lymphadenopathies (bilateral cervical, axillary, retroperitoneal, iliac and inguinal lymph nodes) and active
29 lymphomatous nodules in bilateral adrenal glands, bilateral epididymis and right testis (**Figure 1**). Then a CT-
30 guided fine needle aspiration cytology (FNAC) of the right inguinal lymph node was done which showed
31 lymphoid cells with foreign body giant cells. No epithelioid tumor or tumor giant cell was seen.

32
33 A histopathological examination was advised for confirmation. A left axillary lymph node biopsy was performed
34 and sent for histopathological examination. Preoperative investigations were normal. Mantoux test and triple
35 serology was negative (HIV, Hepatitis B and C). Histopathological examination of axillary lymph nodes showed
36 multiple epithelioid granulomas with Langhans giant cells and foci of caseous necrosis. (**Figure 2**)
37 Histopathological features were in favor of tuberculous lymphadenitis. A diagnosis of disseminated extra-
38 pulmonary TB with testicular involvement was made.

39 Treatment and Outcome

40 No drug resistance was detected in line probe assay. The patient was started on anti-tubercular treatment of
41 isoniazid, rifampicin, pyrazinamide and ethambutol for two months followed by 4 months of isoniazid, rifampicin

- 1 and ethambutol. During treatment, the patient was followed up at 1 month, 2 months, 4 months, and 6 months.
- 2 The patient underwent full remission. Testicular enlargement and nodularity went down and no pain or
- 3 tenderness were reported further. Lymph node swelling was absent on subsequent visits. The patient now
- 4 follows up regularly every 6 months at the OPD.

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1 DISCUSSION.

2
3 TB can involve many organs like lymph nodes, liver, bone marrow, kidney, testis etc. Acid-fast bacilli may be
4 found in epithelioid cells or inside caseation. Disseminated TB presents with subacute or chronic constitutional
5 symptoms (fever, weight loss and night sweats). It often mimics various conditions like torsion and infarction
6 (painful testicular mass) or cancer (widespread involvement) etc. All of these conditions present with testicular
7 enlargement, lump, with or without color changes. Pain is also a common feature but is usually not present in
8 cancer. Also, pain in testicular TB is chronic compared to sudden onset pain torsion and infarction. Specific
9 features of torsion is elevated testis and the absence of cremasteric reflex. Thus, history taking and clinical
10 examination is important to distinguish between these conditions especially in acute presentations. In testicular
11 masses FNAC is not done due to risk of tumor cell seeding. Only way to do a cytological or histological is an
12 excisional biopsy – This is a significant challenge for the diagnosis of these cases.█

13 The key to differentiate between various differential diagnoses is by diagnostic tests like imaging, microbiological
14 tests, tissue biopsy, etc. Mantoux test is often negative in disseminated TB thus not so reliable.¹ Diagnosis of
15 disseminated TB can be confirmed if any one of the following is present - isolation of tubercle bacilli, positive
16 PCR or Histologic demonstration of caseating granuloma in the biopsy specimen.¹ In our case, the symptoms
17 were first interpreted as an inflammatory condition (epididymo-orchitis) which initially improved with later relapse
18 and testicular nodularity. Testicular neoplasms were suspected but it didn't fit with the diagnostic tests done
19 later. Ultimately it was diagnosed as a disseminated TB with testicular involvement after histologic evidence of
20 caseating granuloma in the axillary lymph nodes. A case similar to ours was reported in a patient by Namburete
21 El *et al.*³ The patient was HIV positive in which case dissemination of TB is common.^{1, 3} However, our patient
22 was immunocompetent without any history of pulmonary disease which makes it unique. Najdawi *et al.* reported
23 a totally opposite situation in a case of non-seminoma germ cell tumor presenting with dyspnea and cavitory
24 lung lesions which mimicked TB.⁴ Xiao described a case of testicular TB which was diagnosed after orchiectomy
25 as malignancy was suspected and extensive damage to the testis.⁵ Mohamed Ali *et al.* described two cases of
26 testicular tuberculosis from Somalia in immunocompetent patients.⁶ One had a history of respiratory TB while
27 other one didn't. Muttarak M *et al.* described a case where the diagnosis was based on ultrasonography, no
28 response to conventional antibiotics, and response to first line anti-TB drugs.⁷ All of this exemplifies the
29 complexity of diagnosing this condition and the various other conditions it seems to mimic, such as infarction,
30 cancer, torsion, etc.³ In clinical practice, the presentation and history can vary widely as discussed above.
31 Absence of history of any respiratory illness doesn't necessarily rule out the existence of TB as in our case and
32 the one reported by Xiao, Mohamed Ali *et al.*, and Muttarak M *et al.* This can be a challenge when a patient
33 presents acutely with the complaints of pain in testes, enlargement and color changes. Histopathology is likely
34 the most effective method to differentiate these conditions as seen in our case and other reported cases.²⁻⁵
35 Medical management by anti-TB drugs is the mainstay of treatment but sometimes surgical management
36 becomes necessary.⁸ This case contributes to the existing literature on disseminated TB and will help clinicians
37 to be more aware and cautious while diagnosing conditions with testicular lesions.

1 **SUMMARY - ACCELERATING TRANSLATION**

2

3 A 21-year-old male presented with bilateral testicular enlargement. Initially it was diagnosed as epididymo-
4 orchitis. Further investigations revealed nodules, thickening and lymphadenopathy. Later on MRI was done and
5 testicular lymphoma was suspected. The PET-CT confirmed multiple active lymphadenopathies and nodules.
6 Axillary lymph node biopsy was done which lead to a diagnosis of disseminated extra-pulmonary tuberculosis
7 with testicular involvement. The patient responded well to anti-tubercular treatment. This case highlights the
8 complexity of diagnosing disseminated TB and underscores the importance of histopathological examination
9 for confirmation in atypical presentations. Similar and opposite cases have been reported in the literature
10 exemplifying the complexity and importance of these types of cases. Recognizing these cases is essential as it
11 reduces the risk of complications if treatment is initiated early.

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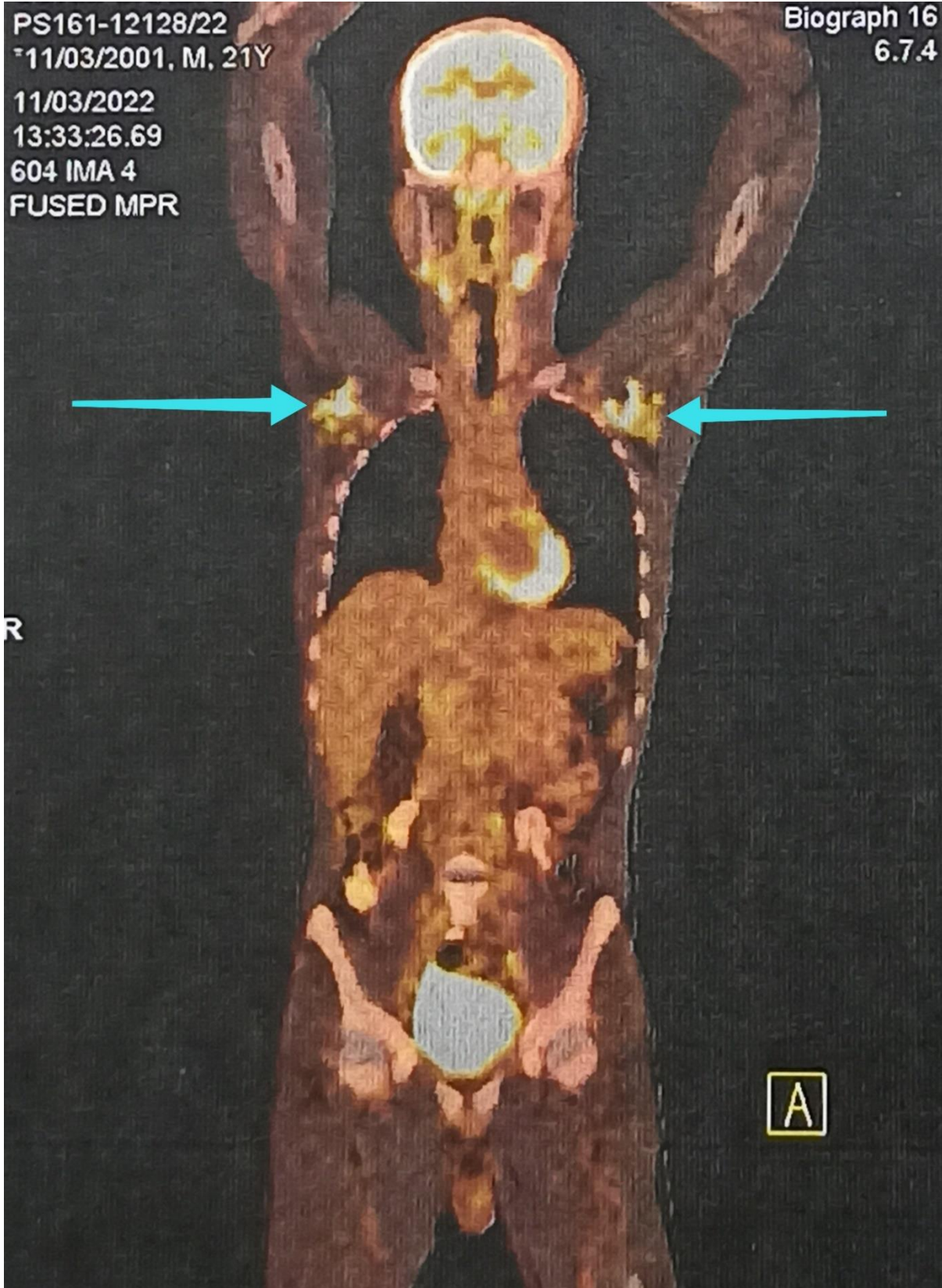
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1 **FIGURES AND TABLES.**

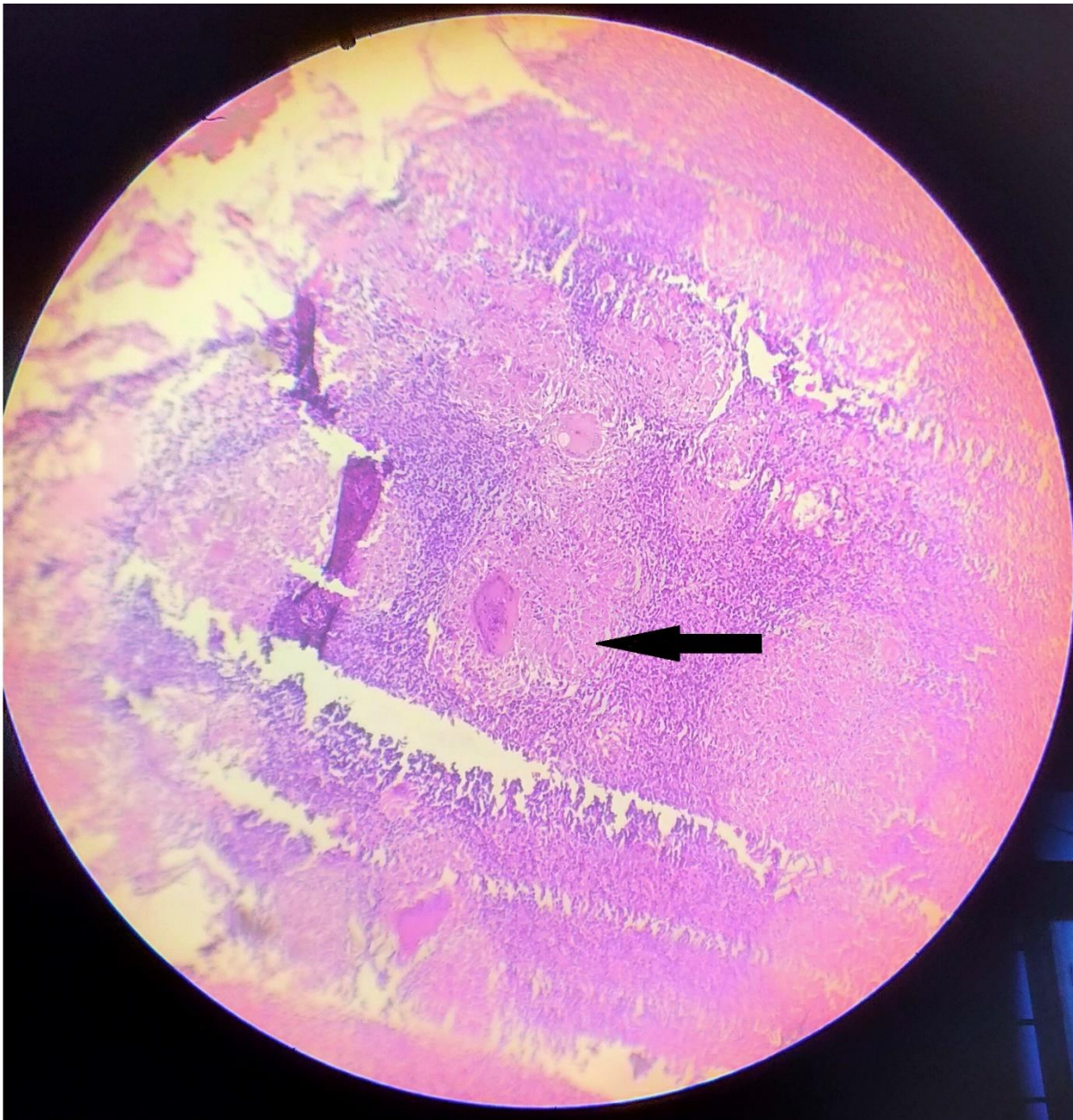
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3 **Figure 1.** Positron emission tomography with computed tomography showing metabolically active axillary lymph
4 nodes (Blue Arrow). It was done after malignancy was suspected to determine the extent of spread.
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- 2 **Figure 2.** Histopathological Examination of Axillary Lymph Node Showing Caseating Granuloma (black arrow).
- 3 This confirmed the diagnosis of tuberculosis.
- 4



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- 6

- 1 **Table1:** Chronological Order of Diagnostic Tests, Findings, and Inferences [MRI – Magnetic resonance imaging,
2 CT – computed tomography, FDG – Fluorodeoxyglucose, PET – Positron emission tomography, TB -
3 Tuberculosis]

Date	Diagnostic tests	Findings	Inferences
4 th August 2021	Clinical examination (Initial)	Both testes were tender, hard and enlarged with loss of sensation	Epididymo-orchitis suspected
19 th August 2021	Clinical examination (Follow up)	Nodularity of right testis and thickening of spermatic cord	Non seminoma germ cell tumor with spermatic cord invasion suspected
14 th September 2021	Testicular tumor markers	Normal	Diagnosis of cancer was in doubt
22 nd October 2021	MRI of pelvis and scrotum	Ill-defined T2 hypointensities in both testes along with multiple perifocal satellite hypo-intense lesions. Similar involvement in the epididymis and bilateral spermatic cord (more on the right side). A mild right-sided hydrocele was noted. Also, mildly increased fluid in the left testis was observed.	Testicular lymphoma was suspected
23 rd December 2021	¹⁸ FDG whole-body PET-CT	Metabolically active multiple lymphadenopathies (bilateral cervical, axillary, retroperitoneal, iliac and inguinal lymph nodes) and active lymphomatous nodules in bilateral adrenal glands, bilateral epididymis and right testis.	Metastasis of suspected testicular lymphoma
11 th March 2022	CT-guided Fine Needle Aspiration Cytology of right inguinal lymph node	Lymphoid cells with foreign body giant cells. No epithelioid tumor or tumor giant cell was seen.	Histopathological analysis suggested

19 th May 2022	Histopathology of axillary lymph nodes	Multiple epithelioid granulomas with Langhans giant cells and foci of caseous necrosis	Disseminated TB with testicular involvement
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