DIAGNOSTIC VALUE OF CYTOLOGICAL EXAMINATION OF PLEURAL FLUID IN TUBERCULOSIS

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ABSTRACT

BACKGROUND

Tuberculosis is a worldwide health problem with highest incidence in developing countries like India. It involves a large number of organs including lungs, pleural lymph nodes, genital sytem, gastrointestinal tract, etc. In resource poor countries, cytological examination of pleural fluid serves as a rapid, effective, economical and easy method of diagnosing tubercuolus pleural effusions, which can be correlated with other newer ancillary techniques.

MATERIALS AND METHODS

The present study was conducted on 100 patients coming to Patna Medical College and Hospital, Patna, over a period of two years from August 2012 to September 2014 with clinical complaints of cough, fever and chest pain with a clinical diagnosis of tuberculous pleural effusion.

RESULTS

Pleural tapping was done and detailed cytological examination of pleural fluid was done and its findings were correlated with gross, biochemical and microbiological findings. Both wet fixed (Giemsa stained) and air-dried slides (Papanicolaou stained) were prepared and microscopic examination was done. Special stains like Ziehl-Neelsen stain (ZN stain) for acid-fast bacilli was also performed for confirmation.

CONCLUSION

Cytological smears revealed predominance of lymphocytes. Mesothelial cells were absent or nearly absent. Eosinophils followed mesothelial cell pattern and were absent in a relatively large number of cases. This technique is safe, reliable, cost-effective and can be used for diagnostic purposes. It is also less traumatic as compared to pleural biopsy. Cytological examination when combined with other newer diagnostic test increases the chances of accurate diagnosis of tuberculous pleural effusion.

KEYWORDS

Tuberculosis, Cytology, Pleural Effusion, Diagnostic, Lymphocytes, Mesothelial.

HOW TO CITE THIS ARTICLE: Jamal I, Dwivedi RP, Singh RVN. Diagnostic value of cytological examination of pleural fluid in tuberculosis. J. Evid. Based Med. Healthc. 2018; 5(1), 4-12. DOI: 10.18410/jebmh/2018/2

BACKGROUND

Tuberculosis remains a worldwide health problem especially in developing countries despite the fact that the causative organism was discovered more than 150 years ago and highly effective drugs and vaccines are available making. According to WHO, nearly one-thirds of world population is exposed to tuberculous pathogen. It affects 1.7 billion individuals worldwide with 8-10 million new cases and 1.7 million deaths each year.[1] It is estimated that 8.5 million new cases occurred in 2001, 95% of them being in Asia, Africa and Middle East (Arlene et al, 2004).[2] Tuberculosis is the most common opportunistic infection and cause of death among HIV positives. Involvement of pleura is common in primary pulmonary TB and results mainly from penetration by tubercle bacilli into pleural space, but rarely can occur by haematogenous route.

Light et al in 1977 classified pleural effusion into two categories- transudate and exudate. Tubercular pleural effusion can manifest as primary or reactivated disease. Rupture of subpleural focus is the main pathogenetic event. Identifying tuberculosis in body fluid is still a common clinical problem. Sheet anchor of diagnosis of TB is demonstration of acid-fast bacilli by either light microscopy or by culture. Unfortunately, bacteriology is positive only in 20% of cases of pleural effusion and culture is also positive in fewer cases. The diagnosis of pleural effusion is also challenging because of lack of amount of sample volume, non-uniform distribution of microorganism and presence of inhibitors that undermine the performance of amplification-based techniques. Demonstration of AFB in fluids also not always fruitful, since positivity rate in body fluid is low (Karron et al, 1947).[3] Pleural fluid aspiration with pleural biopsy is advised for investigation of pleural effusion. Pleural fluid is analysed for cellular content, chemistry, culture of microorganism and cytology. Cytology is the recent tool supporting the diagnosis of many diseases. Cytological diagnosis is the art and science

Financial or Other, Competing Interest: None.
Submission 11-12-2017, Peer Review 18-12-2017,
Acceptance 26-12-2017, Published 01-01-2018.
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DOI: 10.18410/jebmh/2018/2

of interpretation of cells from human body that either exfoliate freely from epithelial surface or are removed from various tissue sources by various clinical procedures (Koss,1979).[4] Cytology has ceased to be an adjunct to other methods of diagnosis rather it has become primary source of information in many fields of medicine. Cytology is not a substitute of biopsy, but maybe made equally reliable especially in situations where biopsy isn't possible. As in other diagnostic methods, it is practically impossible to avoid all errors in cytological diagnosis.

In the present day, body fluids are subjected to cytological examination. The technique is beneficial to the patient since removal of fluid is not only diagnostic, but also has got therapeutic importance. This work has been taken with an aim to correlate the cytological accuracy with demonstration of AFB in sputum, which is the surest sign of tuberculous infection. The real reason behind this study is that cytological technique is cheaper, quicker and less expensive. It is also less traumatic as compared to pleural biopsy. The main purpose and emphasis of this study was to find out the value of cytological diagnosis in tuberculous pleural effusion.

Aims and Objectives

1. The study was carried out to find out the diagnostic value of cytological examination of pleural fluid in tuberculosis.
2. It showed a correlation of cytological accuracy with demonstration of acid-fast bacilli in the sputum samples of tuberculous patients.
3. It also laid emphasis on the fact that the cytological technique is cheaper, quicker, less traumatic and highly yielding.
4. The cytological technique is also beneficial to the patients as it does not have got only diagnostic importance, but also therapeutic importance.
5. Cytology serves as a complete diagnostic modality, which aims at pointing out the aetiology of effusion as well as prognosis of disease.
6. Cytological examination when combined with other newer diagnostic tests increases the chances of accurate diagnosis of tuberculous pleural effusions.

MATERIALS AND METHODS

The present study was conducted on patients coming to Patna Medical College and Hospital, Patna, over a period of two years from August 2012 to September 2014. Total 100 cases were selected for the study.

Inclusion Criteria- For this study, those patients with pleural effusion have been included in the study who had AFB present in the sputum.

The Plan of Work- A detailed clinical history of the patients followed by clinical and laboratory investigations were done. All relevant laboratory examination including total and differential count of WBC and ESR was done. Examination of sputum for AFB by ZN staining method. A detailed cytological analysis of aspiration of pleural fluid was performed and the findings were correlated with other biochemical and newer ancillary tests, Figure 5- Flowchart showing method of approach to tuberculous pleural effusion patients.

Technique for Collection of Pleural Fluid- The patient was advised to lean forward resting his or her head and arms on a pillow placed on the top of table. The site selected for puncture was guided by clinical and radiological findings. As a rule, this was at the 7^{th}, 8^{th} or 9^{th} intercostals space in posterior axillary line. Prior to aspiration, all needles and syringes were sterilised. Proper aseptic and antiseptic dressing of the proposed site was done using spirit and Betadine. Using a 2 mL hypodermic needle, a wheal was raised on the skin with 3 mL lignocaine (10% solution). The needle was then withdrawn and reintroduced through the centre of wheal at right angle to the skin and midway between two ribs. The lower border of rib was avoided because of the risk of damaging intercostal neurovascular bundle. The subcutaneous tissue, intercostal muscle and parietal peritoneum were successfully infiltrated with local anaesthetic. The aspiration needle was attached to a 50 mL syringe and introduced through the wheal. There was loss of resistance when tip of needle pierced the pleura. Fluid was withdrawn slowly from the pleural space up to a maximum volume as far as practicable. If no fluid was obtained at the first attempt, the direction and depth of needle was altered. At the end of drainage, the needle was withdrawn and the puncture site was sealed with tincture benzoin.

The pleural fluid was then transferred into 3 aseptic test tubes-

i. Tube containing 15 mg fluoride and oxalate (1 part sodium fluoride and 3 parts of potassium oxalate)- 5 mL of fluid collected for sugar and protein detection.
ii. A plain tube (without anticoagulant) for observation of clot.
iii. Tube containing 15 mg EDTA for cytological examination.

Following examinations were done with pleural fluid.

Physical Examination

1. Appearance of fluid.
    a. Normal pleural fluid is pale or straw coloured.
    b. Turbid due to increase in cells and debris.
    c. Cloudy due to presence of infection.
    d. Bloody due to trauma or in malignancy.
    e. Milky in chylothorax.
2. Observe the plain test tube for examination of clot in the pleural fluid.
    a. Normal fluid doesn't clot.
    b. Formation of clot indicates a substantial inflammatory reaction and presence of fibrinogen due to capillary wall damage.
    -Cobweb coagulation is specific for tuberculosis.
    c. Specific gravity- if <1.012- Fluid is transudate.
    If >1.012- Fluid is exudates.
    Increase in specific gravity is mainly due to high protein content (>3 g/dL).

3. Chemical examination-
   <a> Protein- if >3 gm/dL- Exudate.
   If <3 gm/dL- Transudate.
   <b> Glucose- Glucose was determined by glucose oxidase method.
   Normal- 70-110 mg/dL.
   If <40 mg/dL- Denotes bacterial infection, malignancy.
4. Total WBC Count- A count >1000 per cubic mm and more than 50% neutrophils suggest bacterial infection.

A high percentage of lymphocytes suggest TB, lymphoma and carcinoma.

Cytological Examination- Collected fluid was centrifuged at 600 g for 10 minutes. Smears were made from the deposits on prelabelled slides. Two of the slides were wet fixed in 95% of alcohol. One slide was kept for Romanowsky stain (Giemsa stain). The slide fixed in 95% alcohol was stained by Pap method. Slides were mounted in DPX and examined under low power and high power of microscope using 10x eyepiece. Special stains like Ziehl-Neelsen stain were used to demonstrate acid-fast bacilli in the pleural fluid. Cytological examination revealed plenty of mature lymphocytes and macrophages with paucity of mesothelial cells, oeosinophils and neutrophils. Few granulomas and epithelioid cell clusters were also identified on microscopy with lacy proteinaceous background that also favours tuberculous pleural effusions (Figure 6-10). Special staining with Ziehl-Neelsen staining was also done to confirm the presence of acid-fast bacilli (Figure 11).

RESULTS AND OBSERVATIONS

Age (Years)	Number of Cases	Percentage
Below 10	6	6
Above 10 to 20	17	17
Above 20 to 30	28	28
Above 30 to 40	26	26
Above 40 to 50	15	15
Above 50	8	8
Total	**100**	**100**

Table 1. Distribution of Cases on the Basis of Age (n=100)

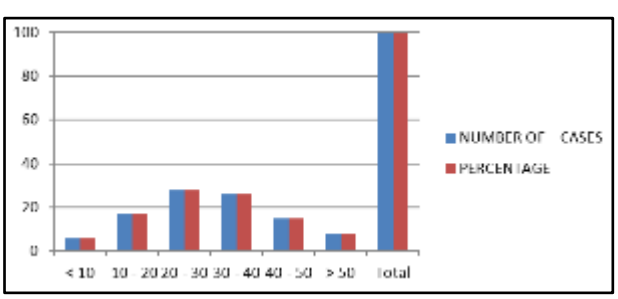

Figure 1. Histogram Showing Percentage and Number of Cases of Tuberculous Pleural Effusion

Among 100 cases selected for study, 54% were in the age group of 21 to 40 years.

Sex	Number of Cases	Percentage
Male	56	56
Female	44	44
Total	**100**	**100**

Table 2. Showing Sex Distribution (N=100)

The above table shows that 56% cases were males and 44% were females.

Figure 2. Histogram Showing Sex Wise Distribution

Religion	Number of Cases	Percentage
Hindu	71	71
Muslim	28	28
Christian	1	1
Total	**100**	**100**

Table 3. Distribution of Cases on the Basis of Religion (N=100)

This table shows that incidence in Hindus was highest 71%, followed by Muslims (28%).

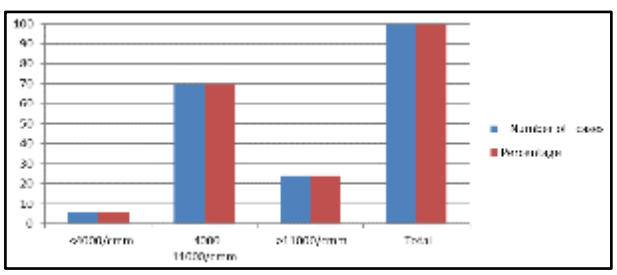

Figure 3. Bar Diagram Showing Total Leucocyte Counts in Tuberculous Pleural Effusion

WBC Range	Number of Cases	Percentage
<4,000/cmm	6	6
4,000-11,000/cmm	70	70
>11,000/cmm	24	24
Total	**100**	**100**

Table 4. Showing WBC Count in Peripheral Blood (N=100)

This table shows that 70% cases have WBC count within normal range; 6% were leucopenic, whereas 24% had leucocytosis.

ESR - Ist Hour Reading by Westergren Method (mm)	Number of Cases	Percentage
21 to 40	9	9
41 to 60	47	47
61 to 80	34	34
81 to 100	8	8
101 to 120	2	2
Total	**100**	**100**

Table 5. Table Showing ESR (N=100)

This table shows that none had normal ESR. 81% had between 41 to 80 mm.

Induration (mm)	Number of Cases	Percentage
Less than 5	6	6
More than 5 to 9	8	8
More than 9	86	86
Total	**100**	**100**

Table 6. Showing Induration in Mantoux Test (N=100)

This table shows 86% had positive Mantoux test, whereas 8% had doubtful result and 6% had negative Mantoux test.

Specific Gravity	Number of Cases	Percentage
>1.018	77	77
<1.018	23	23
Total	**100**	**100**

Table 7. Showing Specific Gravity of Pleural Fluid (N=100)

This shows that 77% cases had specific gravity >1.018.

Cobweb Coagulation	Number of Cases	Percentage
Present	62	62
Absent	38	38
Total	**100**	**100**

Table 8. Showing Presence of Cobweb Coagulum (N=100)

This table shows that cobweb coagulum was present in 62% cases.

Protein (gm/dL)	Number of Cases	Percentage
Up to 1	2	2
>1 and up to 2	5	5
>2 and up to 3	14	14
>3 and up to 4	12	12
>4 and up to 5	33	33
>5	34	34
Total	**100**	**100**

Table 9. Showing Protein Level in Pleural Fluid (N=100)

This table shows that 79% cases have protein >3 gm/dL and 21% cases have <3 gm/dL.

Glucose Level (mg/dL)	No. of Cases	Percentage
20-40	5	5
41-60	30	30
61-80	63	63
81-100	2	2
Total	**100**	**100**

Table 10. Showing Glucose Level in Pleural Fluid (N=100)

This table shows that 63% cases have glucose level >60 mg/dL.

Table 11 showing cytological observation in pleural fluid (N=100).

Type of Cells Observed in Pleural Fluid	Number of Cells (Range)
Lymphocytes	80-95
Neutrophils	15-4
Oeosinophils	1-0
Mesothelial cells	1-0
Epithelioid cells	2-1
Others	1-0

Table 11. Shows Percentage of Different Types of Cells Observed in Tuberculous Pleural Effusion

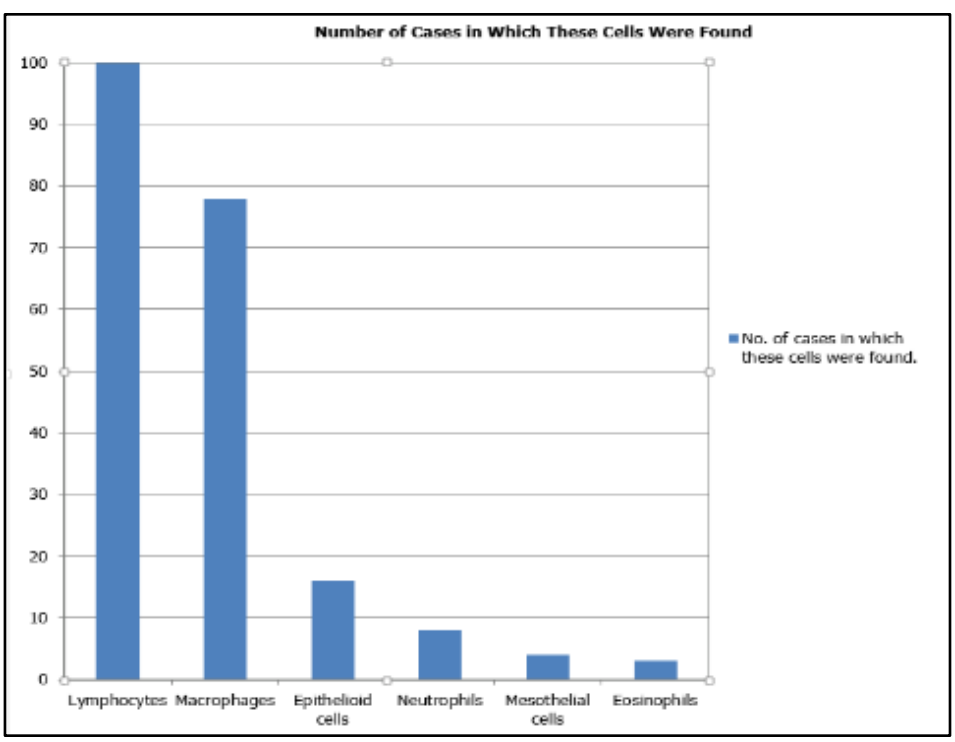

Figure 4. Showing Variation in Number of Different Cells Found in Tuberculous Pleural Effusion

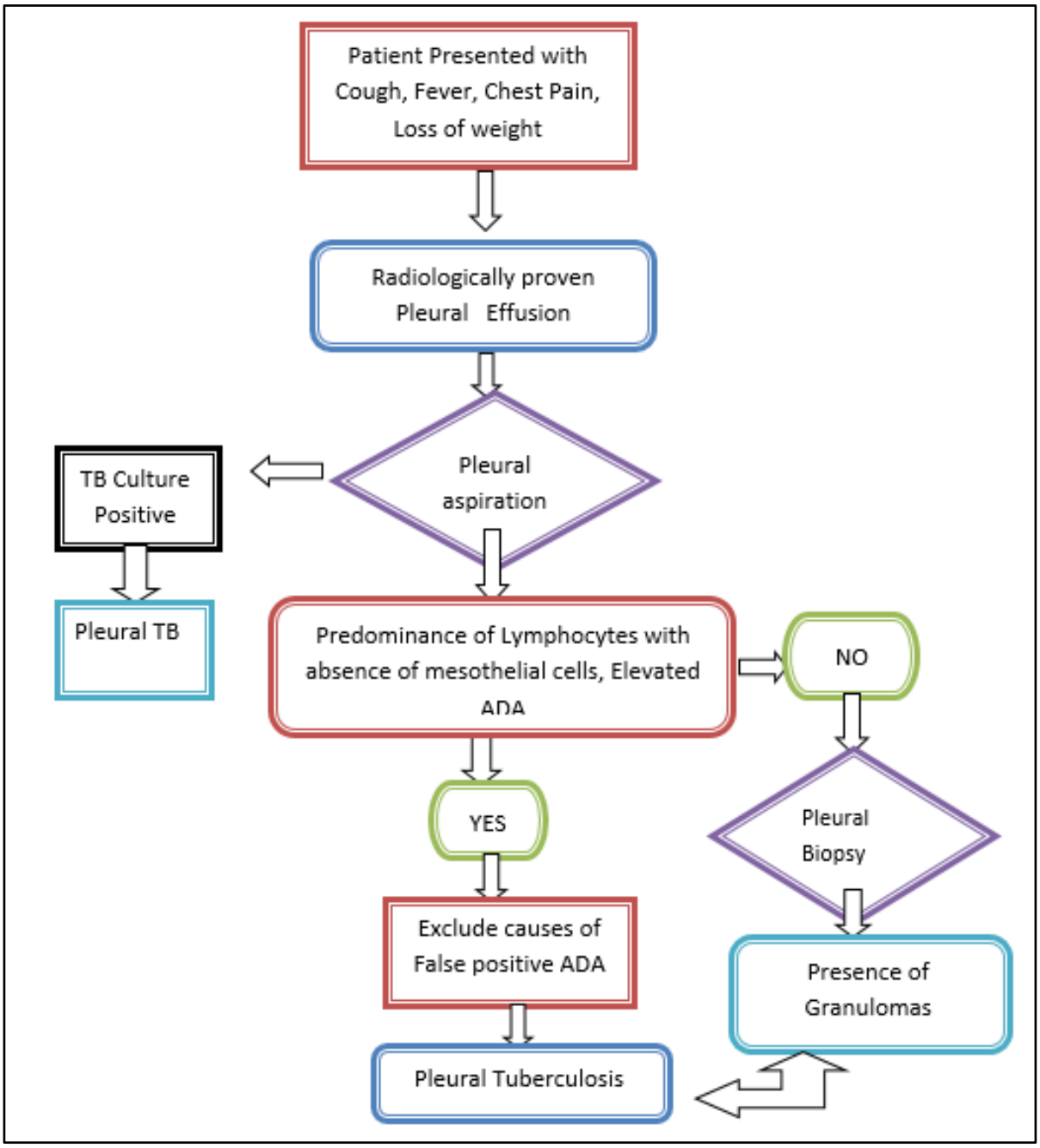

Figure 5. Flowchart Showing Method of Approach to Tuberculous Pleural Effusion Patients

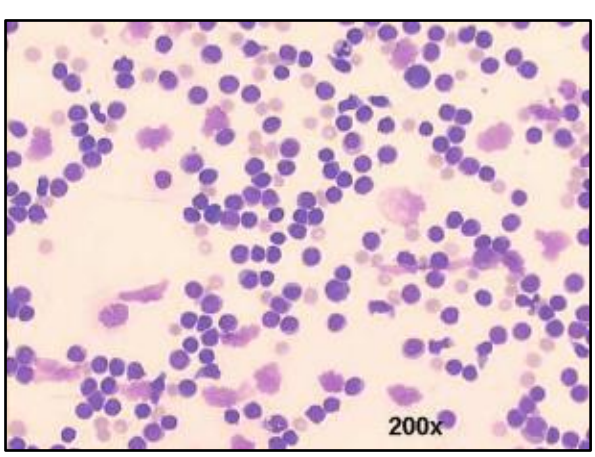

Figure 6. Cytological Examination of Pleural Fluid Showing Predominantly Lymphocytes in Tuberculous Pleural Effusion (Giemsa Stain)

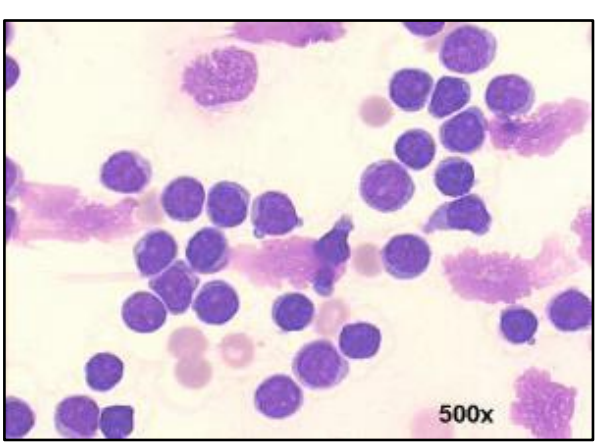

Figure 7. Higher Magnification Showing Predominance of Lymphocytes in Tuberculous Pleural Effusion (Giemsa Stain)

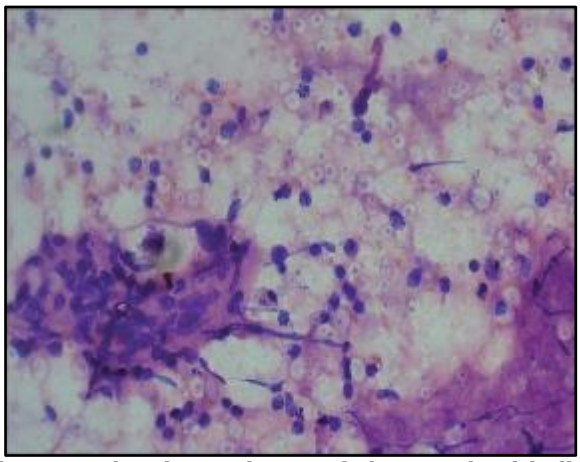

Figure 8. Showing a Cluster of Elongated Epithelioid Cells along with Lymphocytes (Giemsa Stain)

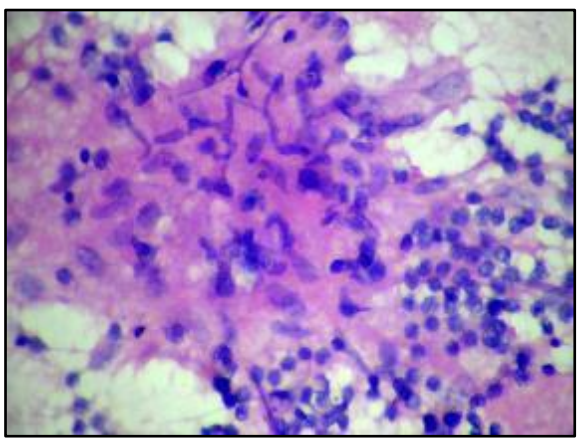

Figure 9. Higher Magnification Showing Elongated Spindle-Shaped Epithelioid Cells Along with Lymphocytes in Tuberculous Pleural Effusion (Giemsa Stain)

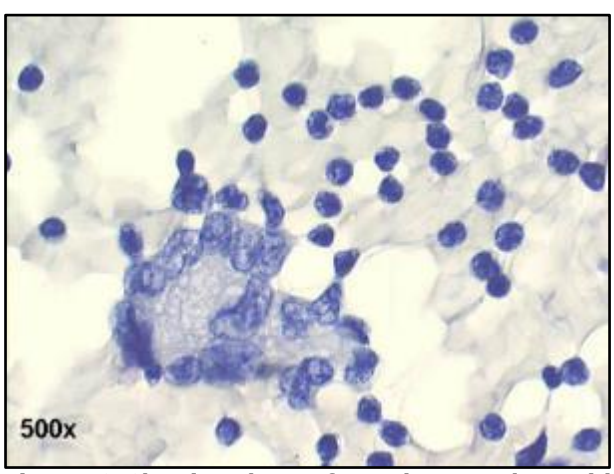

Figure 10. Showing Plenty of Lymphocytes along with Few Epithelioid Cells, Multinucleated Langhans Type Giant Cells and no Mesothelial Cells (Pap Stain)

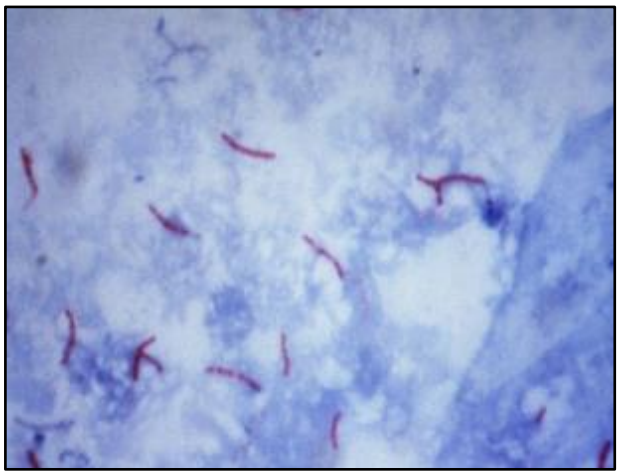

Figure 11. Microscopic Examination of Sputum showing Acid-Fast Bacilli Positivity (by Ziehl-Neelsen Staining)

DISCUSSION

In recent times, cytological studies have been found valuable as an aid to diagnosis in various fields of medicine. The use of cytology for the diagnostic purposes has increased much after the work of Papanicolaou. In the literature of cytology, there is little known about the diagnosis of TB. It would be of great value if any cell changes indicating the presence of TB could be identified. This would be of considerable importance in the clinical differential diagnosis of various lung diseases, particularly of pulmonary TB from other lung diseases. The cytological examination of cells in pleural fluid was done to find out that whether it can help in establishing early diagnosis of TB, thus starting early treatment, which result in less spread of the disease. For this, 100 cases of tuberculous pleural effusions confirmed by demonstration of AFB in their sputum were studied. Table 1 shows 54% of cases belong to the age group of 21-40 years. In the present series, youngest patient was 3 years old and oldest patient was 72 years old. The incidence in children and young adults was 23%. It is in agreement with Hasseling et al (2002) who reported the incidence of 15-20% in this age group. The incidence is highest in adolescent and young adults. Many workers have reported that pleural effusion occurred more often in adolescents and young adults (Fargacs et al, 1957; Polland, 1959).[5] These are in accordance with age incidence in present study. The increase in incidence in adults may be attributed to the fact that there is recrudescence of an old infection due to reduced immunological surveillance by T-lymphocytes.

Table 2 and 12 shows sex distribution in cases of tuberculous pleural effusion examined. There were 56% male cases, which indicates the male predominate females in pulmonary tuberculosis. The reason for higher incidence in males is not exactly known. It may be due to higher risk of coming in contact with the infectious agent.

Comparative study of distribution of pleural effusions according to sex.

Authors	Female	Male	Ratio
Prakash UBS et al, 1985	41.79%	58.21%	1:1.39
Sherwani R et al, 2005	64.6%	35.4%	1.82:1
Khan et al, 2005	56.9%	43.%	1.32:1
Present study	44%	56%	1:1.27

Table 12. Showing Comparison of Various Studies done in Past with the Present Study

Table 3 shows the distribution of tuberculous pleural effusion on the basis of religion. Hindus were in majority 71%, followed by Muslims 28%, which were followed by 1% Christians. This finding is consistent with the distribution of different religions in the population of Bihar.

Table 4 shows variation in WBC count in peripheral blood. Peripheral blood leucocyte count was in normal range in 70% cases. Leucocytosis was observed in 24% of cases, whereas mild leucopenia seen in 6% of cases. A normal total WBC count in presence of extensive pulmonary shadow in chest radiograph favours diagnosis of tuberculous pleural effusion (Gordan et al, 2002).

Table 5 shows variation in ESR in cases of tuberculous pleural effusion. It shows that ESR is raised in all cases. It is indirect diagnostic evidence. It is an old dictum that in chronic disease, ESR is increased due to increase in fibrinogen and globulin concentration of plasma.

Table 6 shows the response to Mantoux test. Infection with Mycobacterium tuberculosis typically leads to the development of delayed hypersensitivity that is detected by Mantoux test. It is being used since 1941 as a screening test for TB. The test is of limited value in diagnosis of active TB because of its low sensitivity and specificity. It has no role in differentiation between disease and infection (Alexander et al, 2004).[6] In the present study, Mantoux test is positive in 86% cases, while 6% cases give negative result. Thus, majority of cases gave positive result, which is in agreement with the above. Donald et al, 1984, reported a similar incidence of Mantoux positivity.[7]

Table 7 shows the variations in specific gravity of cases of tuberculous pleural effusion examined. It shows that majority of cases have specific gravity greater than 1.018. Specific gravity has a good correlation with osmolality of pleural fluid. Similar findings were recorded by Poddock (1940). Increase in specific gravity is mainly due to high protein content (Godkar et al, 2003).[8]

Table 8 shows the presence of cobweb coagulum in pleural fluid. 62% showed the presence of cobweb coagulum, while 38% cases showed the absence of cobweb coagulum. Normally, pleural fluid does not clot, but in certain diseases because of rise in protein content of fluid, clots are observed. Cobweb coagulum or fine spider web coagulum is characteristic of tuberculosis.

Table 9 shows the presence of protein in pleural fluid. It shows majority of cases have protein more than 3 g/dL. This is in accordance with Mario et al, 2005, who found that protein concentration of pleural fluid is more than 50% of the serum protein level.[9]

Table 10 shows the glucose levels of tuberculous pleural fluid. It was in the range of 61-80 mg/dL in majority of cases, which is quite close to normal blood glucose level. It is in accordance with Mario et al, 2005, and Richard et al, 2005.[10]

Table 11 shows different cell population in cytological smears. Cells in pleural fluid are mainly lymphocytes and all lymphocytic cells being enlarged with slight indentation of their nuclei and splintering of nuclear chromatin. Other cells which are present in small numbers are neutrophils, oeosinophils, plasma cells, giant cells and epithelioid cells. Neutrophil count in pleural fluid of tuberculous effusion was low. In a study by Burgess LJ et al (1995), pleural fluid.

Lymphocyte/neutrophil ratio 0.75 or greater was used as a combined parameter for diagnostic confirmation of TB.[11] Mesothelial cells are generally rare or absent in tuberculous pleural effusion (Mario et al, 2005; Richard et al, 2005).[12] Mesothelial cells are important for diagnosing tuberculosis. Their absence is almost always a pointer towards Tuberculosis unless proved otherwise. More diminution in number of mesothelial cells should raise suspicion of tuberculosis. Oeosinophils mimics the same pattern as that of mesothelial cells. They were present in only 67% cases in a very small number. According to various authors, if oeosinophils are found in pleural fluid in significant numbers (>10%), one can virtually exclude the diagnosis of tuberculous pleuritis, unless the patient has pneumothorax or has had a previous thoracocentesis.

The presence of epithelioid cells is also seen in tuberculous pleural effusion. They are seen in cases where a subpleural granuloma has bursted into pleural cavity. In the present series, they were present in hardly 5% cases.[13] Besides the plasma cells, macrophages were present in all cases, but they were hardly occasional ones and didn't have significant number.

A very characteristic proteinaceous "lacy background" was found in some of the smears of tuberculous pleural effusion cases in present study. Presence of such lacy background is not pathognomonic, but points towards the diagnosis of TPE. It is due to the presence of proteinaceous fibrinous material present in pleural fluids.[14-16]

Comparison of Giemsa and Pap Stains

Features	Giemsa Stain	Pap Stain
Cell and nuclear size	Exaggerated	Comparable to tissue sections
Cytoplasmic details	Well demonstrated	Poorly demonstrated
Nuclear details	Not so well demonstrated	Excellently demonstrated
Nucleoli	Not always discernible	Well demonstrated
Necrotic tissues	Poorly demonstrated	Well demonstrated

Table 13. Showing Comparison of Giemsa and Papanicolaou Stain

Lymphocytic exudates seen in TB pleural effusion can also occur in other disease such as- malignancy, lymphoproliferative disorders like Hodgkin's disease and other types of lymphomas, congestive cardiac failure, collagen vascular disease and various inflammatory disorders.

A definitive diagnosis of tuberculous pleural effusion requires the presence of granulomas in pleural tissue or a stained AFB or positive culture from the pleural tissue, pleural fluid[17] or AFB.

Culture is positive in 15-45% of cases of tuberculous pleural effusion. Diagnostic yield increases to 90% when pleural fluid cytology is combined with pleural biopsy and AFB culture.[18-23]

Direct examination of pleural fluid detects AFB in less than 10% of cases.[22-23] Biomarkers that can help distinguish tuberculous pleural effusions from other causes of pleural effusions are Adenosine Deaminase (ADA) and Interferon-γ (IFN-γ). Adenosine deaminase appears to be particularly useful as a screening test with a cut-off of 35 being 93% sensitive and 90% specific. However, false positives are frequent with 70% of empyemas and 57% of lymphomas also producing elevated.

ADA Levels- An ADA level under 40 units/L is said to virtually rule out the diagnosis of TB. Interferon-γ has also been used to aid in diagnosing tuberculous pleural effusions. A meta-analysis published in 2007 revealed that sensitivity 89% and specificity 97%. DNA probes have additionally been used to reveal the presence of tuberculosis, but are marred by a low.

Sensitivity of 62-76.5%, though specificity is 91-97%.[18-23] Other newer tests that have high efficacy in diagnosing tuberculous pleural effusion are polymerase chain reaction and nucleic acid amplification test. Thus, it is apparent from the above that cytological examination of pleural fluid in cases of tuberculosis is a very useful diagnostic tool in the diagnosis of tuberculous pleural effusion. Plenty of lymphocytes with absence or near absence of mesothelial cells and oeosinophils are consistent findings in tuberculous pleural effusion. These findings confirm the basis of treatment of TB in suspected cases of tuberculous pleural effusion. Pleural fluid aspiration as compared to pleural biopsy is less traumatic. This diagnostic technique is economical, quick, cheap, safer and reliable as well.

CONCLUSION

- Cytological smears revealed predominance of lymphocytes. Mesothelial cells were absent or nearly absent. Eosinophils followed mesothelial cell pattern and were absent in a relatively large number of cases.
- This technique is safe, reliable, cost effective and can be used for diagnostic purposes.
- It is also less traumatic as compared to pleural biopsy.
- Cytology serves as a complete diagnostic modality, which aims at pointing out the aetiology of effusion as well as prognosis of disease.
- Cytological examination when combined with other newer diagnostic tests increases the chances of accurate diagnosis of tuberculous pleural effusion.

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