

# To evaluate clinical utility of MUM-1 IHC to detect chronic endometritis due to genital tuberculosis

Ashita Punjabi<sup>1</sup>, Rana Mondal<sup>1</sup>, Jharna Mishra<sup>2</sup>, Pallavi Agrawal<sup>3</sup>, Priya Bhawe Chittawar<sup>3</sup>

<sup>1</sup>FNB Reproductive Medicine, Bansal Hospital, Bhopal, Madhya Pradesh

<sup>2</sup>Department of Pathology, Bansal Hospital, Bhopal, Madhya Pradesh

<sup>3</sup>Department of Reproductive Medicine, Bansal Hospital, Bhopal, Madhya Pradesh

## Abstract

**Introduction:** Due to its paucibacillary nature, diagnostic tests to detect genital tuberculosis (GTB) suffer from low detection rate. Endometrium is involved in about 50% cases of GTB. Multiple myeloma 1 transcription factor immunohistochemistry (MUM-1 IHC), a marker of plasma cells, has been shown as a sensitive marker for detecting chronic endometritis. **Aim:** The aim of this study is to evaluate the clinical utility of MUM-1 IHC to detect endometrial involvement and chronic endometritis in GTB. **Materials and Methods:** This was a retrospective study conducted in a reproductive medicine unit. Three hundred ninety-one infertile patients who underwent hysterolaparoscopy and in whom MUM-1 IHC was done in the period from May 2019 to December 2020 were included in the study. Diagnosis of GTB was made on laparoscopic findings of tubercles, caseation, dense pelvic adhesions, encysted fluid, tubo-ovarian mass, and cornual blockage in accordance with index tuberculosis (TB) guidelines for extrapulmonary TB in India. **Results:** Sixty cases of GTB were diagnosed based on laparoscopic findings. Out of 60 patients, MUM-1 IHC was positive in 28 cases and negative in 32 cases. GeneXpert was negative in all 60 cases of laparoscopy-diagnosed GTB. Histopathology was positive in nine cases of GTB. Sensitivity and specificity of the test are 46.66 and 85.80%, respectively. **Conclusion:** MUM-1 IHC can be proven as a useful marker to rule out endometrial involvement in GTB owing to its high specificity and can be recommended in conditions in which histopathology and GeneXpert are negative; however, prospective studies are needed to confirm the findings of the present study.

**Keywords:** Genital tuberculosis, Multiple myeloma 1 transcription factor immunohistochemistry, Chronic endometritis

**Address for correspondence:** Dr Ashita Punjabi, Department of Reproductive Medicine, Bansal Hospital, Bhopal 462016, Madhya Pradesh, India.


E-mail: ashpunjabi@gmail.com

**Submission:** 21-12-2022, **Revised:** 17-04-2023, **Accepted:** 17-04-2023, **Published:** 30-June-2023

## INTRODUCTION

World Health Organization (WHO) in 1993 declared tuberculosis (TB) as a “Global Emergency” considering its significant impact on individual’s health and wider social and economic consequences.<sup>[1]</sup> *Mycobacterium tuberculosis* is the etiological agent for TB. Female genital

tract TB is a leading cause of infertility, especially in developing countries. Being silent in nature, it causes massive destruction of genital structures till it is diagnosed. It is usually secondary to a primary focus elsewhere in the body. The fallopian tubes are involved in 90% to 100% of cases, endometrium is involved in 50% to 80% of cases, ovaries in 20% to 30%, and cervix is

Access this article online	
<b>Quick Response Code:</b> 	<b>Website:</b> <a href="http://www.fertilityscienceresearch.org">www.fertilityscienceresearch.org</a>
	<b>DOI:</b> 10.4103/fsr.fsr_35_22

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

**How to cite this article:** Punjabi A, Mondal R, Mishra J, Agrawal P, Chittawar PB. To evaluate clinical utility of MUM-1 IHC to detect chronic endometritis due to genital tuberculosis. *Fertil Sci Res* 2023;10:94-7.

involved in 5% to 15% cases of genital tuberculosis (GTB).<sup>[2]</sup> Incidence of GTB varies widely ranging from 1% in infertility clinics of USA to 1% to 19% in various parts of India.<sup>[2-4]</sup>

Being paucibacillary in nature, diagnostic tests to evaluate GTB suffer from low detection rate. Culture methods are considered as the gold standard in the detection of GTB. Conventional media such as Löwenstein–Jensen medium requires 1000 bacilli/mL and takes up to 6 to 8 weeks to provide results. Liquid-based culture media such as BACTEC 460 provide results within 2 weeks and provide rapid assessment for drug sensitivity patterns.<sup>[5]</sup> Polymerase chain reaction (PCR) is a rapid, sensitive, and specific method that can detect <10 bacilli/mL of the sample and results are available within 1 to 2 days,<sup>[6]</sup> but it suffers from high false positive and false negative rates.

Laparoscopy involves operative and anesthetic risks and risk of infection [Figure 1].

CD 138 is widely used as an ancillary immunohistochemistry stain to identify plasma cells; however, it has a drawback of high background reaction. Multiple myeloma 1 transcription factor immunohistochemistry (MUM-1 IHC) has been shown to be a more sensitive stain than CD 138 in diagnosing chronic endometritis in addition to having clean background.<sup>[7]</sup>

Since endometrium is involved in almost half of the cases of genital TB, we sought to evaluate MUM-1 as a marker of endometrial involvement and chronic endometritis due to GTB.

## MATERIALS AND METHODS

### Ethical Clearance

The study was conducted after taking ethical clearance from the Institutional Human Ethics Committee, Bansal Hospital, Bhopal, Madhya Pradesh (BH006).

This was a retrospective study conducted in a Reproductive Medicine Unit. Three hundred ninety-one infertile patients who underwent hysterolaparoscopy and in whom MUM-1 IHC was done in the period from May 2019 to December 2020 were included in the study.

The primary outcome measure of the study was to evaluate MUM-1 IHC as a marker of endometrial involvement and chronic endometritis due to GTB. The cases were diagnosed on the basis of definite laparoscopic findings such as tubercles, caseous nodules, or probable findings such as dense pelvic

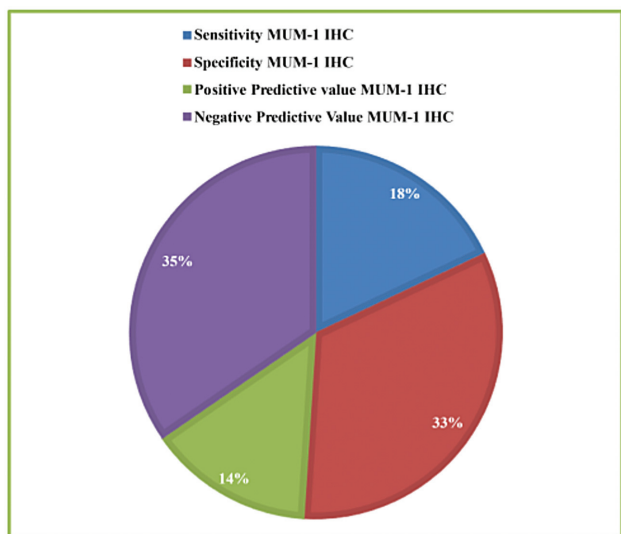


Figure 1: Sensitivity and Specificity of MUM1-IHC.

Table 1: Sensitivity and Specificity of MUM-1 IHC

	MUM-1 IHC Positive	MUM-1 IHC Negative
GTB cases	28	32
Non-GTB cases	47	284
Sensitivity MUM-1 IHC		46.66%
Specificity MUM-1 IHC		85.80%
Positive predictive value MUM-1 IHC		37.33%
Negative predictive value MUM-1 IHC		89.87%

GTB=genital tuberculosis, MUM-1 IHC= multiple myeloma 1 transcription factor immunohistochemistry

Table 2: Comparison between Histopathology, GeneXpert, and MUM-1 IHC

	MUM-1 IHC (%)	Histopathology (%)	GeneXpert (%)	Chi-square	P value
Sensitivity	46.66	15	0	34.538	0.000000004
Specificity	85.80	100	99.39		
Positive predictive value	37.33	100	0		
Negative predictive value	89.87	86.64	84.57		

adhesions, peritoneal or perihepatic adhesions, encysted fluid, tubo-ovarian mass, congested or convoluted tubes, and cornual blockage.<sup>[8]</sup>

Following hysterolaparoscopy, endometrial samples were sent for MUM-1 IHC and cartridge-based nucleic acid amplification test (CB-NAAT) in normal saline and histopathological examination in formalin.

For MUM-1 IHC, ready to use monoclonal mouse antibody is used to label formalin fixed, paraffin-embedded tissue sections. The staining steps and incubation times are programmed into the software of DAKO Autostainer. Cells labeled by the antibody display predominantly nuclear staining, although weak to moderate staining of the cytoplasm is also present in most cases with nuclear staining.

A value of “1” was assigned to a positive stain if at least one plasma cell had been observed. A value of “0” was given to a negative stain if no plasma cell was detected in the respective endometrial tissue section value.<sup>[7]</sup>

### Statistical Analysis

For continuous data, the descriptive statistics was used such as mean and standard deviation. Frequency and percentage were used for categorical data. Microsoft Office Excel 97 to 2003 was used for tabulation of data and statistical analysis.

## RESULTS

Mean age of women was  $32.24 \pm 0.26$  years. Sixty cases of GTB were diagnosed based on hysterolaparoscopic findings. Out of 60 patients, MUM-1 IHC was positive in 28 cases and negative in 32 cases [Table 1]. GeneXpert was negative in all 60 cases of laparoscopy-diagnosed GTB. Histopathology was positive in nine cases of GTB.

## DISCUSSION

Diagnosis of GTB poses a great challenge owing to its paucibacillary nature and varied clinical features. Culture is considered as a gold standard but paucibacillary nature of GTB can lead to negative culture. In study by Sharma *et al.*, adhesions were present in 88.8% women. Other findings were beading of tubes, presence of tubercles, caseation, and tubo-ovarian masses.<sup>[9]</sup> The index TB guidelines on extrapulmonary TB in India guide for diagnosing GTB based on laparoscopic appearance

typical for TB.<sup>[10]</sup> In the present study, cases of GTB were diagnosed on laparoscopy.

Delay in treatment can cause significant morbidity and can have serious repercussions on the fertility of women. Endometrium is involved in almost half of the cases of GTB. Endometrial involvement can destroy endometrium causing Asherman syndrome. Therefore, there is a need to evaluate diagnostic modalities, which can diagnose endometrial involvement in GTB so treatment can be started at the earliest to prevent progression of the disease.

MUM-1 is a lymphocyte-specific transcriptional factor, a member of interferon regulatory factor (IRF) family. It contributes to the regulation of immunoglobulin gene expression in the final step (late centrocyte) of B-cell differentiation within germinal center. MUM1 is not only a marker for plasma cells, but also highlights activated B and T cells; or only lymphoid cells in an activated state.<sup>[11]</sup> Physiologically, B lymphocytes tend to aggregate in the basalis layer and constitute approximately 1% of the normal lymphoid population. In endometritis, the B cells increase in the endometrium aggregating in the functionalis rather than the basalis layer with no significant change in the T-cell population.<sup>[12,13]</sup> Therefore, the presence of the MUM1-positive lymphoid B cells in the endometrial stroma may be a clue for the presence of active inflammation versus normal or physiological conditions.<sup>[7]</sup> Recently, a new concept of impaired inflammatory state of endometrium has emerged instead of chronic endometritis, which considers both infectious factors (*Streptococcus*, *Escherichia coli*, *Enterococcus*, GTB, etc.) and noninfectious factors (endometriosis, adenomyosis, endometrial polyp, autoimmune, and hormonal disturbances) unlike chronic endometritis which only refers to infectious pathology.<sup>[14]</sup>

To our knowledge, the present study is the first study to evaluate MUM-1 IHC as marker of endometrial involvement and chronic endometritis in GTB. Sensitivity and specificity of the test are 46.66% and 85.80% respectively. Sensitivity of histopathology is 15% and specificity is 100% in our study, whereas GeneXpert has 0% sensitivity and 99.3% specificity [Table 2]. Garg *et al.*<sup>[15]</sup> did not find any patient positive with GeneXpert among 81 infertile women suspected of having GTB as a cause of infertility.<sup>[15]</sup> MUM-1 has a good negative predictive value along with hysterolaparoscopy in ruling out endometrial involvement and chronic endometritis due to TB.

Limitations of the study include its being retrospective in nature which could have introduced bias in the study and small sample size.

## CONCLUSION

MUM-1 IHC can be proven as a useful marker to rule out endometrial involvement in GTB owing to its high specificity and can be recommended in conditions in which histopathology and GeneXpert are negative; however, prospective studies are needed to confirm the findings of the present study.

## Financial support and sponsorship

There has been no financial vested interest.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Global Tuberculosis Control: Surveillance, Planning, Financing. WHO Report; 2008.
2. Sharma JB. Female genital tuberculosis revisited. *Obstet Gynaecol Today* 2007;XII:61–3.
3. Parikh FR, Nadkarni SG, Kamat SA, Naik N, Soonawala SB, Parikh RM. Genital tuberculosis—a major pelvic factor causing infertility in Indian women. *Fertil Steril* 1997;67:497-500.
4. Gupta N, Sharma JB, Mittal S, Singh N, Misra R, Kukreja M. Genital tuberculosis in Indian infertility patients. *Int J Gynecol Obstet* 2007;97:135-8.
5. Katoch VM. Newer diagnostic techniques for TB. *Indian J Med Res* 2004;120:418-28.
6. Shetty J, Kumar P, Ramkumar V, Dhott AK. Management of female genital tuberculosis: re-appraised. *Obstet Gynaec Today* 2006;11:506-9.
7. Parks RN, Kim CJ, Al-Safi ZA, Armstrong AA, Zore T, Moatamed NA. Multiple myeloma 1 transcription factor is superior to CD138 as a marker of plasma cells in endometrium. *Int J Surg Pathol* 2019;27:372-9.
8. Sharma JB, Sharma E, Sharma S, Singh J, Chopra N. Genital TB-diagnostic algorithm and treatment. *Indian J Tuberc* 2020;67: S111-8.
9. Sharma JB, Roy KK, Pushparaj M, *et al.* Genital tuberculosis: an important cause of Asherman's syndrome in India. *Arch Gynecol Obstet* 2008;277:37-41.
10. Sharma SK, Ryan H, Khaparde S, *et al.* Index-TB guidelines: guidelines on extrapulmonary tuberculosis for India. *Indian J Med Res* 2017;145:448-63.
11. Falini B, Fizzotti M, Pucciarini A, *et al.* A monoclonal antibody (MUM1p) detects expression of the MUM1/IRF4 protein in a subset of germinal center B cells, plasma cells, and activated T cells. *Blood* 2000;95:2084-92.
12. McCluggage WG. Benign diseases of the endometrium. In: Kurman RJ, Ellenson LH, Ronnett BM, eds. *Blaustein's Pathology of the Female Genital Tract*. New York, NY: Springer 2011; p. 307–58.
13. Disep B, Innes BA, Cochrane HR, Tijani S, Bulmer JN. Immunohistochemical characterization of endometrial leucocytes in endometritis. *Histopathology* 2004;45:625-32.
14. Drizi A, Djokovic D, Laganà AS, van Herendael B. Impaired inflammatory state of the endometrium: a multifaceted approach to endometrial inflammation. *Current insights and future directions. Prz Menopauzalny* 2020;19:90-100.
15. Garg R, Agarwal N, Gupta M. GeneXpert test and endometrial histological findings in infertile women. *Int J Reprod Contracept Obstet Gynaecol* 2018;7:1480-3.