ORIGINAL ARTICLE

Clinical Spectrum of Tuberculosis Otitis Media (TBOM) and Management Outcomes

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ABSTRACT

Objectives. To determine the initial clinical diagnoses of patients with tuberculous otitis media (TBOM), to determine the value of PCR test, biopsy, and ancillary diagnostic procedures in detecting middle ear TB infection, and to establish the differences in treatment outcomes.

Methods. The clinical records of twenty-eight patients identified with middle ear TB infection by PCR test and biopsy, from January 2010 to December 2016, were reviewed to determine their initial clinical diagnoses. The positivity rates of PCR test and biopsy were compared. The records of 12 patients included in a previous publication were revisited and included in the present study population. The combined cases were classified according to clinical diagnosis to constitute a summary of demographic characteristics, clinical diagnoses, laboratory tests, and treatment outcomes. Results of diagnostic and surgical procedures were reviewed and analyzed. Clinical findings and hearing test results before and after treatment were compared.

Results. Of the 28 patients, eight different clinical diagnoses of patients confirmed with middle ear TB were determined. PCR test diagnosed most cases belonging to the early and chronic stages of the disease process. Biopsy diagnosed mostly the chronic cases but failed to diagnose acute cases and late cases with diagnosis of chronic suppurative otitis media with cholesteatoma. By including the twelve cases that were published in 2011, the range of clinical diagnoses was expanded and an outcome of eleven clinical diagnoses confirmed with TB infection was established. Analysis of treatment outcomes showed that the clinical and hearing outcomes were better for patients managed at the early stage of the disease than for those presenting at the late stages of the disease process who underwent more complicated surgical procedures.

Conclusion. Our study supports the concept of tuberculous otitis media (TBOM) clinical spectrum, implying a paradigm shift in the established thinking that TBOM presents only as a chronic disease. The combined use of PCR and biopsy is a potential diagnostic tool to improve case detection rate, further broaden the scope of the clinical spectrum, and develop better control and preventive strategies for TBOM.

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INTRODUCTION

Tuberculous otitis media (TBOM) is difficult to diagnose because of its rarity, varied presentations and lack of distinguishing clinical features.[1-4] Consequently, most TBOM reports were diagnosed intraoperatively or postoperatively, from specimen obtained mostly among chronic otitis media cases,[4-6] oftentimes, resulting to late diagnosis and treatment. The low prevalence rate of less than 1% among chronic suppurative otitis media[7], and the absence of associated

systemic involvement in majority of cases[6] further contribute to the impossibility of diagnosing TBOM in the absence of laboratory findings[8].

The basis for diagnosing middle ear tuberculous (TB) infection can be any of the following: positivity to acid fast bacilli (AFB) stain, culture growth of Mycobacterium tuberculosis (M.Tb), histologic finding of TB granuloma on biopsy, and positive polymerase chain reaction (PCR) test for M.Tb.[6] Though M.Tb culture is considered the gold standard for diagnosis, the complexities of the test and the delay in obtaining the result make the test less popular.[8] By contrast, AFB stain is inexpensive, readily available but insensitive.[9] The commonly employed histopathologic examination has limited sensitivity even in confirmed TB cases if the classic TB granuloma is not identified in the submitted specimen.[9] PCR M.Tb is rapid, sensitive, and widely accepted.[9] Remarkably, despite the presence of these different tests, laboratory examinations for TBOM are regarded as unreliable[4] probably because of inadequate knowledge regarding their specific usefulness and limitations.

The Philippines is included among the ten countries in the world where tuberculosis is considered a public health problem.[10] In this kind of environment, many clinical manifestations of TBOM may indeed be varied and remain unrecognized based on disease pathogenesis.[11] To provide more information regarding this concern and to elucidate on disparities on the role of various diagnostic tests in TBOM, we aim to describe the clinical presentations of middle ear tuberculosis derived from clinical practice, provide data on the possible role of PCR M.Tb and biopsy relative to the different clinical diagnoses, and to report on our treatment outcomes.

METHODS

We reviewed the clinical records of TBOM patients seen in a tertiary private hospital, from 2010-2016, in Manila, Philippines. This case series included the twelve cases that were in the 2011 publication[3] who presented with otitis media with effusion, middle ear mass-like lesions with thickened eardrum, multiple eardrum perforations, chronic otitis media with granulation tissue formation, and chronic otitis media with dry perforation. Due to the increased awareness about the possibility of TB infection as possible cause of failure or complication after middle ear reconstructive surgery, the principal author adopted the practice of submitting middle ear mucosal specimens for routine biopsy and middle ear or mastoid antral washing for TB PCR Test, whether the diagnosis was acute or chronic otitis media. In addition, otitis media cases seen at the clinic with atypical presentation, had unusual frequent recurrences, unsuccessfully treated by several accredited specialists, and unexplained responses to optimal antibiotic therapy, became suspect for the possibility of middle ear TB infection and were provided with further laboratory investigations.

The study was approved by the Institutional Review Board of the Manila Doctors Hospital. All study subjects were private patients treated and operated by the principal author. PCR test for Mycobacterium tuberculosis (PCR M. Tb) and biopsy were used in a non-random manner, depending on the availability of specimen. Liquid specimen gathered from clinic patients who were assessed at the early stage of otitis media infection were submitted for PCR test alone. At surgery, mucosal or soft tissue specimen obtained from the middle ear or mastoid cavity were submitted to biopsy. Approximately 3 to 5 ml of middle ear or mastoid NSS washing were aspirated and submitted for PCR test.

A total of 135 patients with otitis media underwent PCR Test / biopsy in the period of 2010 -2016. Of these, 28 patients were identified with middle ear TB infection based on PCR TB test and/or biopsy, and their records were reviewed. Likewise, the records of the 12 patients reported previously[3] were revisited to determine their respective clinical diagnosis, gather their laboratory results and data related to treatment. To compare the positivity rate of PCR and biopsy for each clinical category, only the data of 28 patients identified in the present study were included in the analysis. The data of the patients that were published earlier were combined with the present study to provide a summary of the demographic characteristics, clinical diagnoses, laboratory results, and treatment outcomes.

Participants and demographic characteristics

The clinical diagnoses of patients were based on clinical history and otoscopic findings as proposed by Harkness.[12] Primary cases with non-suppurative acute otitis media (AOM) were initially treated medically with oral antibiotic for 2-3 weeks. Acute suppurative otitis media (ASOM) cases were treated with oral antibiotics ± quinolone ototopical drops. Otitis media with effusion (OME) cases were given one-week oral steroid ± antibiotic regimen. Chronic suppurative otitis media (CSOM) without cholesteatoma were treated initially with aural toilet and quinolone ototopical drops for 2-4 weeks depending on the clinical response. CSOM with cholesteatoma were advised surgery. Cases with atypical presentations but with clinical history compatible with middle ear infection were likewise treated initially with oral and/or topical antibiotic. Suspicion on the possibility of middle ear TB infection was entertained among cases unresponsive to optimal medical treatment, or with recurrent disease even after adequate and repeated medical or surgical interventions. More detailed personal, family, and social history of possible TB infection or exposure were obtained for cases suspected of having TBOM. Patients satisfying the need for surgery underwent the commonly accepted surgical procedures. The different surgical interventions for diagnosis and treatment were all performed by the senior author. Consent was secured for human immunodeficiency virus (HIV) test on patients who tested positive for PCR or biopsy. The recorded pre- and post-treatment video-otoscopic pictures that were stored

in a password protected computer file were collected and reviewed. The demographic characteristics and results of biopsy, PCR test, chest x-ray, purified protein derivative skin test (PPD), pure tone audiometry, and temporal bone CT results were gathered, tabulated, and analyzed.

Collection of specimens for biopsy and PCR test

Whenever feasible, otorrhea was aspirated by means of a sterile 3 ml syringe under the operating microscope at the senior author's clinic. Using another sterile syringe, 3 ml of normal saline solution (NSS) was used to irrigate the external auditory canal, thereafter aspirated, whenever the otorrhea was deemed scanty. Under local anesthesia and aseptic method, the middle ear effusion of a patient with either an AOM or OME was collected through the myringotomy incision or the inserted ventilation tube. Similarly, 3 ml sterile NSS was used to irrigate the middle ear to increase the specimen volume, whenever necessary. For patients who underwent middle ear reconstructive surgery, adequate granulation and/or mucosal tissue samples were collected intraoperatively for PCR test and biopsy. The middle ear and/or mastoid cavity were washed with NSS in patients with dry mucosa or inadequate discharge. The washing was collected by sterile syringe and the specimen sent for PCR M.Tb examination.

Anti-tuberculosis drug therapy

Patients who did not undergo middle ear reconstructive procedure received anti-TB drugs soon after the positive result of biopsy or PCR test was known and after being medically cleared to undergo the planned drug therapy. The anti-TB drug regimen was given in accordance with the guideline for extra-pulmonary TB as proposed by the Philippine Task Force on Tuberculosis.[13] This consisted of two-month 4-drug treatment with Isoniazid (INH) 400mg per day, Rifampicin (RF) 600mg per day, Pyrazinamide (PZA) 2 grams per day, and ethambutol 15mg per kg per day, subsequently followed by a four-month 3-drug treatment regimen with INH, RF, and PZA. Patients who underwent middle ear reconstructive surgery received similar anti-TB drug regimen within two weeks after the positive laboratory test result for TB was obtained. Modification of the drug regimen was done for two patients who exhibited drug reaction during treatment.

Outcome measures

Qualitative visual microscopic appearance (intact or perforated) of the tympanic membranes before, and at 3-6 months and 12-18 months after treatment were compared. Pre-and post-treatment pure tone thresholds in decibels (mean, standard deviation) at 500, 1000, 2000, and 4000 Hertz were determined and compared. Post-treatment air and bone threshold levels at the abovementioned frequencies, were taken 3-6 months and 12-18 months after surgery. The difference between air and bone threshold values greater than 10 decibels was considered significant and any difference beyond this level was considered an air-bone gap (ABG). To compare the mean air and bone thresholds, ABG, and ABG closure between patients who did not undergo middle ear reconstructive surgery (Without MER surgery) and those who did, (With MER surgery), the following computations were done:

1. The mean pre-operative and post-operative air and bone conduction thresholds (mean ABG) of patients Without MER Surgery and those With MER surgery were computed. Narrower or smaller pre-operative ABG was interpreted as smaller degree of conductive hearing loss. Larger or wider ABG was interpreted as larger degree of conductive hearing loss.
2. The difference in mean post-operative ABG and pre-operative ABG of each group, termed mean ABG closure, was computed for each group. Larger or wider mean ABG closure value was interpreted as larger post-operative improvement. Correspondingly, smaller or narrower ABG closure value was interpreted as smaller post-operative improvement.
3. The mean ABG closure of patients with no MER surgery was compared with mean ABG closure of patients with MER surgery by using paired t-test.

RESULTS

Demographic characteristics

Eight clinical categories were identified in 28 patients (Table 1) identified with positive PCR and/or biopsy among 135 patients who underwent the tests. Of the 28 patients, there were 12 males and 16 females (M:F = 1:1.33), and age ranged from 5-65 years. The left ear (n=19) was more frequently affected than the right. Three operated patients had bilateral chronic middle ear involvement but the presence of TB infection was confirmed in only one ear.

Table 2 shows that more patients at different categories registered more positive results with PCR than biopsy. PCR

Table 1. Twenty-eight Patients with TB Infection from 141 Patients

Clinical Diagnosis	Positive test for TB	Negative test for TB	Patients tested
1. AOM	1	1	2
2. ASOM	2	3	5
3. AdhOM	2	7	9
4. TMperf dry	5	31	36
5. CSOMnochol	6	29	35
6. CSOMchol	9	35	44
7. Aural polyp	2	1	3
8. Multi TM perf	1	0	1
Total	**28**	**113**	**135**

AOM = acute otitis media, ASOM = acute suppurative otitis media, AdhOM = adhesive otitis media, TM perf dry = tympanic membrane, perforation dry, CSOMnochol = chronic suppurative otitis media without cholesteatoma, CSOMchol = chronic suppurative otitis media with cholesteatoma, Multi perf = multiple eardrum perforations

Table 2. Distribution of PCR and Biopsy Positivity Rates (n=28)

Clinical Diagnosis	PCR+	No. tested	Rate (%)	Biopsy +	No. tested	Rate (%)
1. AOM	1	2	50	NA	NA	NA
2. ASOM	2	5	40	NA	NA	NA
3. AdhOM	2	9	22.22	NA	NA	NA
4. TMperf dry	4	31	12.9	1	23	4.76
5. CSOMnochol	5	36	19.44	3	34	8.82
6. CSOMchol	9	44	2.45	0	0	0
7. Aural polyp	1	3	33.33	2	2	100
8. Multi TM perf	0	1	0	1	1	100
Total	**24**			**8**		

AOM = acute otitis media, ASOM = acute suppurative otitis media, AdhOM = adhesive otitis media, TM perf dry = tympanic membrane, perforation dry, CSOMnochol = chronic suppurative otitis media without cholesteatoma, CSOMchol = chronic suppurative otitis media with cholesteatoma, Multi perf = multiple eardrum perforations, NA = not applicable

was able to detect the presence of TB infection at the early stages of TBOM whose clinical presentation was mainly the secretion of middle ear fluid behind the intact eardrum. Since these early cases were seen in outpatient clinic, it was not possible to gather mucosal specimen for biopsy. On the other hand, biopsy detected the presence of TB in chronic cases who underwent surgery where soft tissue specimen for biopsy was obtained.

Combining the data in Table 1 with the data obtained in 2011 study, a summary of the results are shown in Table 3. There was increase in the number of clinical diagnoses to eleven and there was increase in the number of patients for the following categories: tympanic membrane perforation dry, chronic otitis media without cholesteatoma, and multiple eardrum perforations, affirming the advantages of doing repeated studies to widen the scope of the middle ear infectious spectrum.

The common chief complaints of the patients were otorrhea (52%), hearing loss (35%), and otalgia (5%). The frequently associated complaints were hearing loss (44.6%), dizziness or imbalance (12.7%), tinnitus (10.6%), and otalgia (4.2%).

Table 3. Distribution of 40 Patients into 11 Clinical Diagnoses

Clinical Diagnosis	Frequency	Percentage
1. Acute otitis media	1	2.5
2. Acute suppurative otitis media	2	5
3. Otitis media with effusion	4	10
4. Adhesive otitis media	2	5
5. Tympanic membrane perforation, dry	6	15
6. Chronic suppurative otitis media (-) cholesteatoma	8	20
7. Chronic suppurative otitis media (+) cholesteatoma	9	22.5
8. Aural polyp	2	5
9. Multiple tympanic membrane perforations	2	5
10. Middle ear mass, thick TM	2	5
11. Thickened, congested TM	2	5
Total	**40**	**100**

Clinical diagnoses

The eleven clinical diagnoses (Table 3) we used were based on the otitis media classification commonly used by otolaryngologists.[12,14] Included in our series are acute otitis media (AOM) in one case (2.5%), acute suppurative otitis media (ASOM) in two cases (5%), and otitis media with effusion (OME) in four cases (10%) which may be considered in the subacute stage of inflammation. Clinical diagnoses indicative of chronic process were more predominant which included adhesive otitis media (5%), tympanic membrane perforation, dry (15%), chronic otitis media with no cholesteatoma (20%), chronic suppurative otitis media with cholesteatoma (22.5%), and aural polyp (5%). Majority of patients in our study had chronic otitis media (active and inactive), than those with acute pathology probably because most cases were derived from patients with chronic conditions operated by the principal author. Notably, while these clinical forms were also seen in patients with non-TB otitis media, there were patients who presented with features that were not included in the OM classification and which appeared typical for TBOM. Interestingly, they were TB granuloma formers confirmed by histopathological examination.

Diagnostic methods: PCR TB and biopsy

In sum, PCR TB test was carried out in 35 of 40 patients (87%) while biopsy was done in 33 (82%). PCR detected TB infection in all patients with AOM, ASOM, adhesive otitis media, tympanic membrane perforation, tympanic membrane perforation, dry, and chronic suppurative otitis media with and without cholesteatoma, but failed to detect TB infection in the two middle ear mass-like specimens that were confirmed positive for TB granuloma. On the contrary, biopsy detected the tuberculous process in all patients with multiple TM perforations and middle ear masses with thick tympanic membranes. There were no middle ear mucosa specimens obtained from patients with AOM, ASOM and adhesive OM. A single case of OME underwent nasopharyngeal biopsy on suspicion of malignancy, which came out positive for TB granuloma and precluded TB PCR test of the middle ear specimen.

PCR was positive in all patients who had CSOM with cholesteatoma, but were reported as cholesteatoma by histopathologic examination. Similarly, all six cases with non-suppurating dry tympanic membrane perforations were diagnosed by means of PCR M. Tb. Of these six cases, biopsy was done in only one because the other five presented with thin, normal-looking mucosa. The single patient who showed dry hyperplastic mucosa underwent biopsy that showed granuloma.

Of the 13 patients with positive histopathologic finding consistent with middle ear TB infection, five (38.46%) were reported as TB granuloma with caseation necrosis with multinucleated Langhan's giant cells, six (46.15%) as chronic granuloma with caseation necrosis, and two (15.38%) as chronic granuloma. Only three patients (one each for multiple TM perforations, dry perforated tympanic membrane, and thick tympanic membrane) showed positive test results for both PCR and biopsy.

Chest radiograph, Tuberculin skin test, and Temporal bone CT scan

The positive chest x-ray results that showed findings indicative of pulmonary TB was found in 14 (35%) patients (Table 4). All patients with multiple tympanic membrane perforations and thick tympanic membrane had positive pulmonary TB, while all patients with CSOM with cholesteatoma, aural polyp, and AOM had negative x-ray findings. Less than 20% of patients with dry tympanic membrane perforation had positive chest x-ray finding.

Eighty percent of patients presented with 10mm or greater skin induration on tuberculin skin test (Table 5). Positive results were detected at different proportions in patients with different clinical diagnoses except for two cases of adhesive otitis media with negative result.

Table 6 shows the temporal bone CT interpretations of 34 patients. The procedures were done in six different hospitals - five in the Philippines and one in the US. There was general lack of uniformity about the radiologic interpretation of results. The most common finding was soft tissue attenuation of the entire middle ear (85.29%). Preserved mastoid air cell architecture with absent sclerosis was found in 17.64% while soft tissue extension to the external canal was noted in less than 10%. Signs of chronic bone changes like eroded ossicles, eroded scutum, mastoid sclerosis, eroded tegmen, and lateral sinus plate were seen in about 30-60%.

Surgical procedures done

Varied procedures were done depending on the purpose of the intervention – diagnostic, removal of cholesteatoma and infected tissues with or without mastoidectomy plus single stage middle ear reconstructive procedure (Table 7). Of the 32 patients who were advised surgery, twenty-three underwent planned single-stage primary mastoidectomy with tympanoplasty with or without autologous graft ossiculo-plasty, while seven had revision surgeries. A cholesteatoma

Table 4. Distribution of PTB Chest Xray Findings according to Clinical Diagnosis, n=40

Clinical Diagnosis	n	(+) n=14	(-) n=26
1. Acute otitis media	1	-	1
2. Acute suppurative otitis media	2	1	1
3. Otitis media with effusion	4	2	2
4. Adhesive otitis media	2	1	1
5. Tympanic membrane perforation, dry	6	1	5
6. Chronic suppurative otitis media (-) cholesteatoma	8	4	4
7. Chronic suppurative otitis media (+) cholesteatoma	9	-	9
8. Aural polyp	2	-	2
9. Multiple tympanic membrane perforations	2	2	-
10. Middle ear mass	2	1	1
11. Thick tympanic membrane	2	2	-
Total	**40**	**14**	**26**
% of Total	**100**	**35**	**65**

Table 5. Distribution of Tuberculin Test Results by Clinical Diagnosis, n=40

Clinical Diagnosis	n	PPD (+)	PPD (-)
1. Acute otitis media	1	1	-
2. Acute suppurative otitis media	2	2	-
3. Otitis media with effusion	4	3	1
4. Adhesive otitis media	2	-	2
5. Tympanic membrane perforation, dry	6	4	2
6. Chronic suppurative otitis media (-) cholesteatoma	8	7	1
7. Chronic suppurative otitis media (+) cholesteatoma	9	9	-
8. Aural polyp	2	1	1
9. Multiple tympanic membrane perforations	2	2	-
10. Middle ear mass	2	1	1
11. Thick tympanic membrane	2	2	-
Total	**40**	**32**	**8**

Table 6. Distribution of Temporal Bone CT Scan Results (n=34)

Temporal bone CT findings	Frequency	%
Soft tissue attenuation entire ME	29	85.29
Preserved mastoid air cell, no sclerosis	6	17.64
Soft tissue extension EAC	3	8.82
Mastoid bone sclerosis	10	29.41
Eroded ossicles	20	58.82
Eroded scutum	16	47.05
Eroded bony labyrinth	0	0.0
Eroded CNII canal	0	0.0
Eroded tegmen	9	26.47
Eroded lateral sinus plate	9	26.47

Table 7. Distribution of Surgical Procedures by Clinical Diagnosis, n=40

Clinical Diagnosis	Procedure	Frequency (%)	Total
1. Acute otitis media	MVT/ Asp	1 (100)	1
2. Acute suppurative otitis media	EAC Asp	2 (100)	2
3. Otitis media with effusion	MVT/Asp NP Bx Expl T/ Asp	2 (50) 1 (25) 1 (25)	4
4. Adhesive otitis media	PMcdTO	2 (100)	2
5. Tympanic membrane perforation, dry	PT PMcuT PMcuTO RMcdTO	1 (16.66) 3 (50) 1 (16.66) 1 (16.66)	6
6. Chronic suppurative otitis media (-) cholesteatoma	PMcuTO PMcuT RMcdTO	3 (37.5) 4 (50) 1 (12.5)	8
7. Chronic suppurative otitis media (+) cholesteatoma	PMcdTO PMcuTO RMcdTO RMcuTO Expl T/ Asp EAC Asp	3 (33.33) 1 (11.11) 2 (2.22) 1 (1.11) 1 (11.11) 1 (11.11)	9
8. Aural polyp	PMcuT Polypectomy/ MVT	1 (50) 1 (50)	2
9. Multiple tympanic membrane perforations	PMcuT PMcuTO	1 (50) 1 (50)	2
10. Middle ear mass	PMcuT PMcuTO	1 (50) 1 (50)	2
11. Thick tympanic membrane	PMcuTO	2 (100)	2

PT = primary tympanoplasty; PMcuT = primary canal up mastoidectomy, tympanoplasty; PMcdTO = Primary Canal Down Mastoidectomy, Tympanoplasty and Ossiculoplasty; PMcuTO = primary canal up mastoidectomy, tympanoplasty and ossiculoplasty; RMcdTO = revision canal down mastoidectomy, tympanoplasty and ossiculoplasty; MVT/Asp = myringotomy, ventilation tube insertion + aspiration of fluid; EAC Asp = Aspiration of external canal fluid; NP Bx = nasopharyngeal biopsy; Expl T/Asp = Exploratory tympanotomy + aspiration of fluid; Polyp/MVT = polypectomy + myringotomy and ventilation tube insertion

patient who refused surgery and opted to receive anti-TB medical treatment after the presence of TB infection was detected by PCR test of external ear canal washing, did not come back for follow up examination. A patient with pre-operative diagnosis of attic cholesteatoma underwent exploratory tympanotomy, had negative intraoperative finding of cholesteatoma, and was diagnosed with TB infection through PCR test of middle ear NSS washing. Facial nerve decompression was done as part of mastoidectomy in one patient with pre-operative facial paralysis.

Minor procedures were done in patients for diagnostic and treatment purposes. This included aspiration of external ear canal exudates in two ASOM, myringotomy with ventilation tube insertion under local anesthesia in one AOM and two OME, and exploratory tympanotomy and aspiration of middle ear fluid in another OME patient. The resolution of OME in a patient whose TB infection was diagnosed by nasopharyngeal biopsy was observed by serial otoscopic evaluation.

Eardrum/ Eardrum graft before and after treatment

The tympanic membrane was perforated in 26 (65%) cases pre-operatively, and reduced to 5 (12%) after treatment (Table 8). Tympanic membrane perforation after treatment was noted in one OME patient who had myringotomy with ventilation tube insertion, and one each in patients with CSOM with and without cholesteatoma, thick tympanic membrane, and aural polyp. Two of the later patients underwent revision surgery for closure of the tympanic graft perforation.

Puretone hearing results before and after treatment

The summary of the mean pre-treatment and post-treatment air-bone gaps (ABG) and their differences at 500, 1000, 2000, and 4000 Hertz are presented in Table 9. The mean air-bone gap difference or closure was larger among cases who were diagnosed at the earlier stages of the disease process (AOM and ASOM). However, due to the small sample sizes of the different categories, hypothesis testing was not performed.

The comparison of pre-treatment hearing results between patients Without MER Surgery and With MER Surgery are shown in Table 10a. The difference in pre-operative mean AC between the two groups was small and not significant (t-test= 0.35). However, the mean pre-operative BC values of patients Without MER Surgery was significantly smaller than

Table 8. Distribution by Eardrum/Eardrum Graft Otoscopic Findings before and after Treatment, n=40

Clinical Diagnosis	Pre-treatment		Post-treatment		Total
	Intact	Perforated	Intact	Perforated	
1. Acute otitis media	1	-	1	-	1
2. Acute suppurative otitis media	-	2	2	-	2
3. Otitis media with effusion	4	-	3	1	4
4. Adhesive otitis media	2	-	2	-	2
5. Tympanic membrane perforation, dry	-	6	6	-	6
6. Chronic suppurative otitis media (-) cholesteatoma	-	8	7	1	8
7. Chronic suppurative otitis media (+) cholesteatoma	1	8	8	1	9
8. Aural polyp	2	-	1	1	2
9. Multiple tympanic membrane perforations	-	2	2	-	2
10. Middle ear mass, thick TM	2	-	2	-	2
11. Thickened, congested TM	2	-	1	1	2
Total	**14**	**26**	**35**	**5**	**40**
% of Total	**35%**	**65%**	**87.5%**	**12.5%**	**100%**

Table 9. Summary of Pre-Treatment and Post-Treatment PTA (500Hz, 1000Hz, 2000Hz, 4000Hz) ABG and difference (n=40)

Clinical diagnosis	Pre-operative mean PTA ABG	Post-operative mean PTA ABG	PTA ABG difference
1. Acute otitis media (n=1)	41.25	8.75	32.50
2. Acute suppurative otitis media (n=2)	40.00	19.38	20.62
3. Otitis media with effusion (n=4)	37.75	33.44	4.31
4. Adhesive otitis media (n=2)	42.50	35.00	7.50
5. Tympanic membrane perforation, dry (n-6)	26.46	23.50	2.96
6. Chronic suppurative otitis media (-) cholesteatoma (n=8)	36.31	26.04	10.27
7. Chronic suppurative otitis media (+) cholesteatoma (n=9)	41.84	39.16	2.67
8. Aural polyp (n=2)	37.50	43.75	-6.25
9. Multiple tympanic membrane perforations (n=2)	27.50	14.38	13.12
10. Middle ear mass (n=2)	41.25	21.25	20.00
11. Thick tympanic membrane (n=2)	15.00	27.50	-12.50

those With MER Surgery, (t-test=0.01), which suggested that the inner ear function of patients who did not need to undergo middle ear reconstructive surgery was better and probably less affected by the early infectious process.

Table 10b shows the mean post-operative ABG of the two groups of patients. The smaller or narrower mean post-operative ABG value of Without MER Surgery was compatible with better middle ear function compared to With MER Surgery group, but the difference was not statistically significant (t=test=0.08)

The larger ABG closure seen in Without MER Surgery patients compared to With MER Surgery group was compatible with larger post-operative hearing improvement as shown in Table 10c. However, the difference was not statistically significant, (t-test= 0.08).

DISCUSSION

Our study shows that in an area with a high prevalence of tuberculosis, TBOM may be detected at the early acute stages of the disease process, as in AOM, ASOM, and OME (Table 3). Such may be found through an active search of cases based on high index of suspicion associated with historical items and laboratory tests.[2,15] The inflammatory condition includes clinical diagnoses that are similarly considered in the more commonly encountered bacterial otitis media, like adhesive otitis media, dry tympanic membrane perforation, chronic suppurative otitis media with and without cholesteatoma, and aural polyp. However, there are also otoscopic presentations like multiple eardrum perforations, middle ear mass-like lesion, and inflamed thickened eardrum that are not typically seen in ordinary bacterial otitis media. Because of the wide commonalities in clinical diagnoses between tuberculous and non-tuberculous otitis media, distinguishing TBOM among otitis media patients is considered difficult and challenging.[15] Our research suggests that rather than looking for the typical features of TBOM, it is better to view and consider its clinical spectrum that both encompasses and extends beyond the clinical diagnoses of the commonly encountered bacterial otitis media. In this regard, a review of its pathophysiology may lessen the difficulties of diagnosis and provide guidelines for better choice of appropriate diagnostic tests.

There are three postulated routes of spread of the tubercle bacilli to the middle ear: through the eustachian

Table 10a. Comparison of Pre-operative Mean ABG Closure between Patients without Middle Ear Reconstructive Surgery (No MER surgery) and with Middle Ear Reconstructive Surgery (With MER surgery)

Audiometric measure	Without MER Surgery (n=7)	With MER Surgery (n=24)	Difference	T-test probability
Preoperative AC PTA mean (SD)	53.93 ± 9.56	59.19 ± 4.22	-5.26 ± 5.56	0.35
Preoperative BC PTA Mean (SD)	14.29 ± 6.61	24.80 ± 2.95	-10.51 ± 3.87	0.01
Preoperative ABG PTA mean (SD)	39.64 ± 6.80	34.39 ± 14.86	5.25 ± 3.67	0.17

Table 10b. Comparison of Post-operative Mean ABG Closure between No MER Surgery and With MER Surgery Patients

Audiometric measure	Without MER Surgery (n=7)	With MER Surgery (n=24)	Difference	T-test probability
Postoperative AC PTA mean (SD)	33.21 ± 11.15	45.36 ± 20.26	-12.15 ± 5.90	0.05
Postoperative BC PTA mean (SD)	13.92 ± 9.69	18.33 ± 24.53	-4.40 ± 4.71	0.36
Postoperative mean ABG PTA (SD)	19.29 ± 8.50	27.03 ± 13.87	-7.74 ± 4.28	0.08

Table 10c. Comparison of ABG Closure between No MER Surgery and With MER Surgery

Audiometric measure	Without MER Surgery (n=7)	With MER Surgery (n=24)	Difference	T-test probability
ABG Closure, mean (SD)	20.36±8.98	6.43±13.90	13.93±4.42	0.08

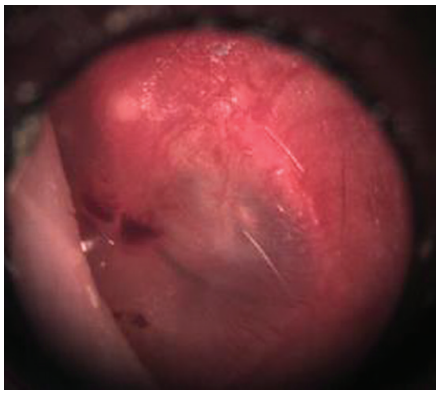

Figure 1. 50/F with acute otitis media, with bulging erythematous TM.

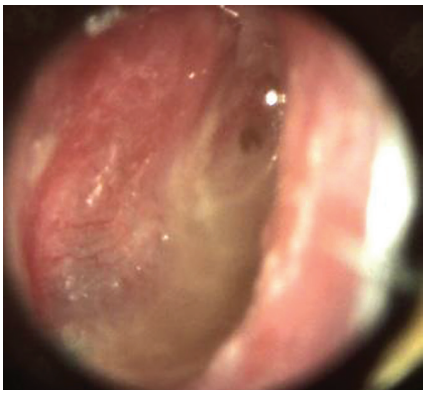

Figure 2. 20/M with acute suppurative otitis media, showing TM perforation.

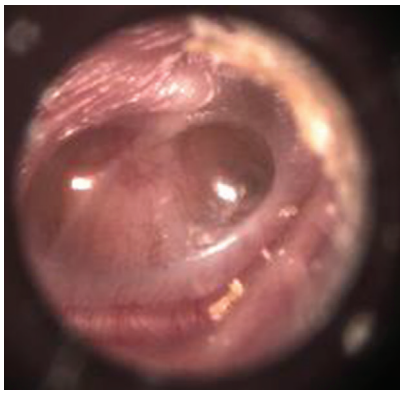

Figure 3. 41/M with OME showing TM retraction pocket.

tube, hematogenous spread through lymphatic channels, and direct extension via the external canal through perforated eardrum.[2,4] Tuberculous infection of the ear typically starts in the marrow spaces of the temporal bone, the mucosa of the middle ear cavity and mastoid air cells, and the tympanic membrane.[4] At the early stage of the infectious process, it is highly possible that the otoscopic presentations of both tuberculous and non-tuberculous otitis media are markedly similar, as those of viral and bacterial etiology.

The typical features of AOM are eardrum erythema, eardrum swelling, and middle ear effusion as seen in our AOM which are usually relieved by proper antimicrobial treatment. Persistence of eardrum congestion and persistence of middle effusion with associated hearing loss and feeling of ear fullness may arouse suspicion of possible etiology, TB infection, as seen in our patient (Figure 1).

Similar findings were earlier reported by Wallner[15] while monitoring by means of otoscopy the clinical progression of 52 presumed TB otitis media patients in two large tuberculosis hospitals in the US in 1953 and by Plester in Germany, in two patients with intact eardrum and serous otitis media.[16] Not much report about this finding was included in later literature probably due to their infrequent occurrence.

Some acute otitis media cases may cause eardrum perforation,[17] thus causing ASOM (Figure 2). The only way to detect TB infection in these cases is to employ laboratory diagnosis on gathered liquid specimen. On the other hand, if the eardrum congestion is relieved but the middle ear effusion persisted for a prolonged unexpected period of time,[18,19] similar laboratory procedure could be employed as in our patients who presented with OME (Figure 3). Thus, because of the close similarity in clinical presentations between acute otitis media cases with and without TB infection, monitoring unexpected deviations in clinical responses to antimicrobial therapy[2] may be the only clinical tool that may trigger further inquiry into the possibility of TBOM.

Like the acute cases, the otoscopic presentations of the chronic cases were quite similar to those found in bacterial,

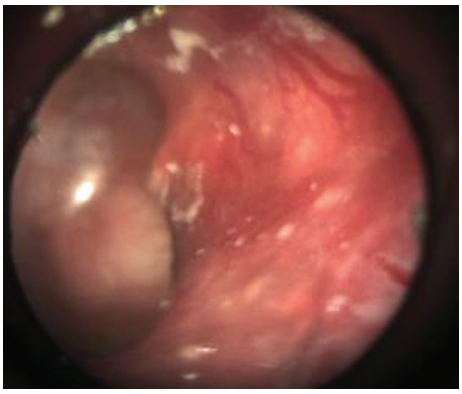

Figure 4. 31/M with adhesive otitis media.

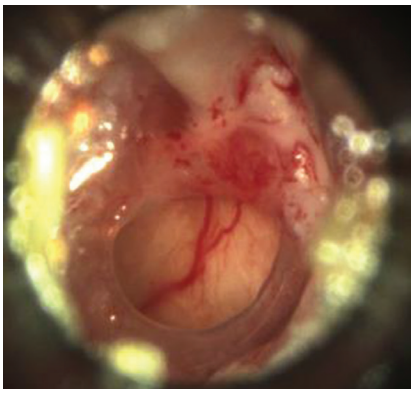

Figure 5. 21/F with dry TM perforation.

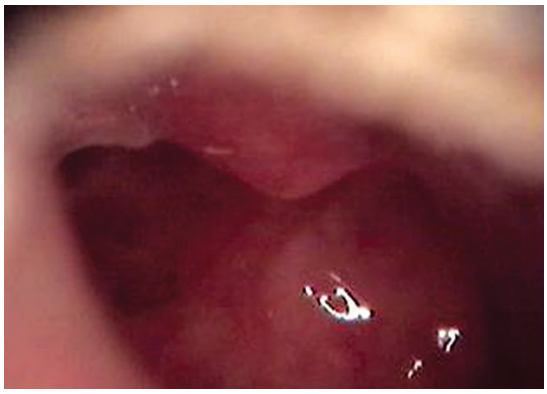

Figure 6. 19/M with CSOM without cholesteatoma.

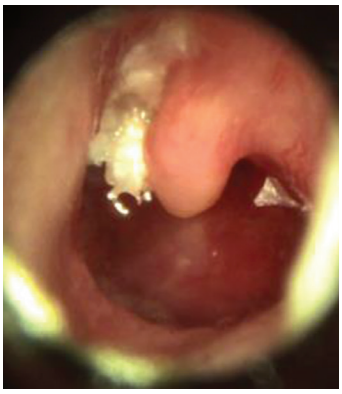

Figure 7. 30/F with CSOM with cholesteatoma.

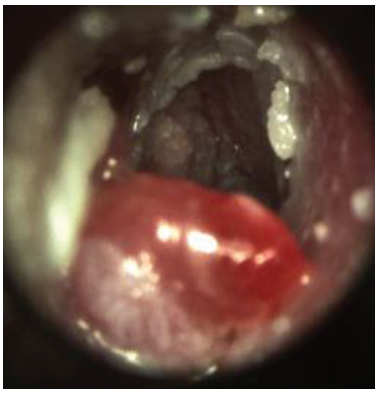

Figure 8. 51/F with aural polyp.

non-TB otitis media. Detection of TB infection among chronic patients was more challenging as in patients who presented with adhesive otitis media, dry TM perforation, CSOM with and without cholesteatoma, and aural polyp (Figures 4-8).

In clinical practice, suspicion of possible TB etiology could be derived on the basis of unexplained recurrence of the disease despite adequate medical and surgical interventions.[8] Though this was true for few cases in our study, the diagnosis of TBOM was largely derived by chance with the use of PCR TB and biopsy.

As the tuberculous infection progresses, the inflammatory process typically proceeds to the stage of delayed hypersensitivity reaction to the TB bacterium. This presents as development of multiple foci of cheese-like foci of necrotic tissues[4] that may get lodged in the eardrum which could soon cause multiple eardrum perforations, as described by Schuknecht[20]. Though considered as the typical clinical presentation of TBOM,[15,21] the concept was contested in later studies because of the rarity of its occurrence[2,3]. The characteristic cheesy ear canal otorrhea in conjunction with multiple eardrum perforations was highly suggestive of a tuberculous etiology, as shown in our study (Figure 9).

The three clinical categories consisting of middle ear mass-like lesion (Figure 10), the congested thickened eardrum (Figure 11), and the multiple TM perforations, that represent TB granuloma formation in the middle ear, as verified by biopsy, were likewise described in earlier reports.[15,16] These clinical features are not typically seen in bacterial otitis media and may be considered distinct clinical features of TBOM (Table 3). Their clinical presentations are based on TB pathogenesis. Their occurrence though infrequent, as seen in only 15% of our study participants, does not negate the concept that they remain as distinguishing feature of TB otitis media. Thus, whenever these features are seen in otitis media patients, active efforts must be made to rule out a tuberculous etiology, particularly, if there are items in history and clinical examination that implicate tuberculosis.

Based on our study, PCR TB test was more useful in identifying the remnants of TB bacilli that could be present in the middle ear fluid at the early stage of infection, as in AOM, ASOM, and OME (Table 2). It was also useful for detecting the presence of TB infection in chronic conditions, as in adhesive OM, dry TM perforation, and CSOM with or without cholesteatoma, based on positive TB PCR results.

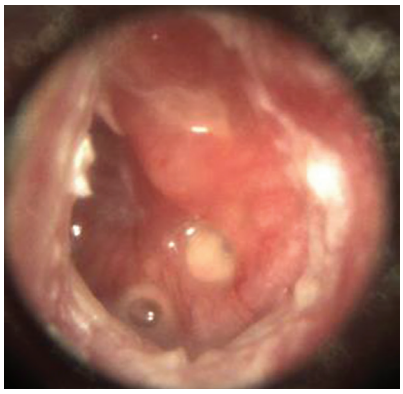

Figure 9. 22/M with multiple eardrum perforations.

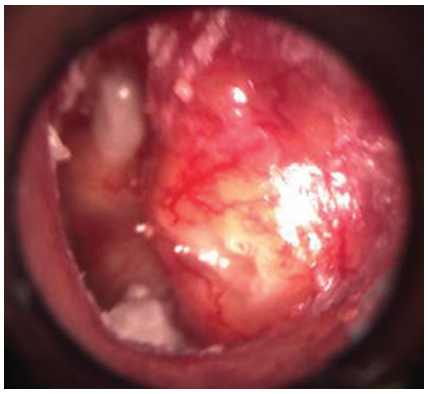

Figure 10. 22/M with middle ear mass-like lesion.

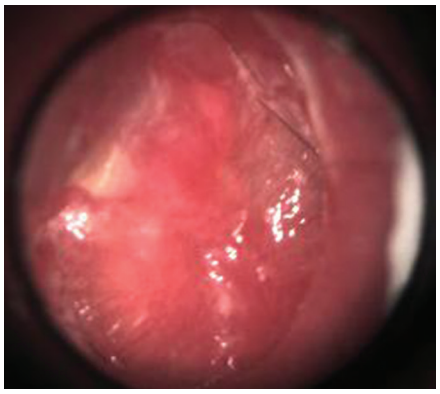

Figure 11. 49/M with thickened eardrum.

The biopsy results of the submitted specimen taken from most chronic cases were reported as chronic inflammatory reaction, which were interpreted as absence of TB granuloma. It is still unknown why some TB cases will form TB granuloma while many will not.[11] On the other hand, regarding the biopsy results of CSOM with cholesteatoma, all were reported as cholesteatoma without mention of concurrent TB granuloma, for unexplained reason. Because of the frequency of CSOM cholesteatoma cases in clinical practice, further studies including Mycobacterium TB culture studies, to answer whether the positivity results to PCR TB found in these cases reflect real infectious process or mere contamination with TB bacilli and to confirm whether patients with chronic inflammatory biopsy reports are indeed negative for TB infection.

In contrast to PCR TB, biopsy was particularly useful in revealing the classic TB granuloma that is indicative of active disease, as in multiple TM perforations, middle ear mass, and thick tympanic membrane. These cases had false negative TB PCR results probably due to the presence of blood that can be an inhibitor of PCR reaction.[22] Since many specimens for confirmatory test were gathered during surgery, the possibility of bloody specimen could not be discounted and may explain why only three patients in our series registered positivity result to both PCR and biopsy. To avoid the submission of bloody NSS washing, it is our experience to do ear canal, or middle ear NSS washing, prior to the surgical procedure, if possible. The false positivity results of PCR indicate that despite its higher detection rate, its combined use with biopsy is more appropriate than using a single diagnostic test alone.

Considering the clinical diagnoses of patients seen in our study and their respective diagnostic test results, our data indicate that within the spectrum of middle ear tuberculosis are three groups of clinical diagnoses. There are two small groups composed of cases reflecting the presence of TB granuloma and another small group representing acute cases. The first group were all diagnosed by biopsy while the second group by PCR TB. The third bigger group is composed of chronic cases who need to be tested by PCR TB and biopsy in order to avoid the false negative results associated with each diagnostic test (Figure 12).

We found selected demographic data, like sex and laterality, not helpful in raising awareness to the possibility of TBOM. Adjunctive laboratory tests were useful in heightening the index of suspicion for TB etiology, as in other reports.[2,3] Obtaining an HIV history, though useful in the light of its increased association to TB incidence was largely lacking in our study. There was a general tendency for our patients to refuse the test and the single patient with middle ear mass submitted a negative result. The presence of soft tissue attenuations in the mastoid and the middle ear seen in 85% of our cases (Table 5) connote that the presence of such findings could also be used as indicators to rule out TBOM. Other CT findings described as parameters[23] for differentiating tuberculous from CSOM with and without cholesteatoma was not appreciated in this study probably because of methodological issues.

The choice among the wide variation in surgical procedures was dictated by the aims of the intervention for each individual case. Minor procedures were found adequate for

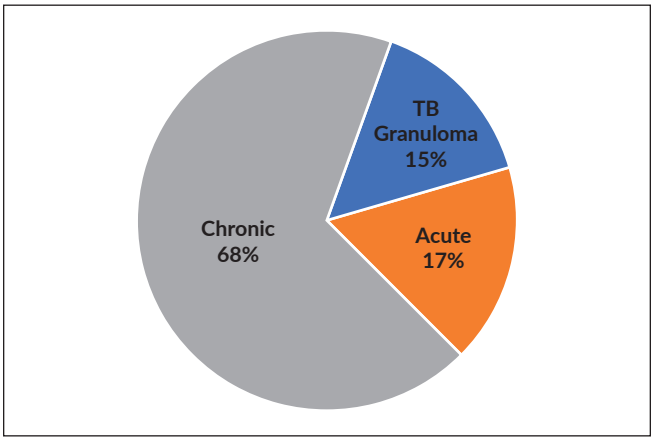

Figure 12. The clinical spectrum of TBOM.

acute cases while chronic cases required more complicated procedures due to the severity of pathological involvement, different degrees of anatomical abnormalities, and need for middle ear reconstructive procedure. For as long as anti-TB drug regimen was given accordingly, post-treatment outcomes were generally favorable in terms of maintaining tympanic membrane integrity, attaining intact eardrum graft, and having satisfactory hearing results (Tables 7 and 8). In sum, the post-treatment hearing results in our study, as measured by ABG closure (Tables 10a-10c), imply that early-staged TBOM patients not needing surgery may elect to take anti-TB therapy prior to surgery if there is no absolute indication for immediate surgical intervention. On the other hand, those needing reconstructive middle ear procedure may still preserve the residual hearing post-operatively (Table 10c), for as long as medical treatment is given to treat the TB infection.

CONCLUSION

Our study provides evidence that tuberculous otitis media is a spectrum of middle ear infectious conditions ranging from acute, subacute, and chronic conditions. This finding challenges the generally accepted concept that tuberculosis is limited to just being a chronic granulomatous process. Our data also affirm our earlier finding that TBOM cases detected at the early stage of the disease need less complicated therapeutic measures and provide better treatment outcomes. These important information were derived because the human middle ear is one of the few organs where the evolution of an infectious process may be directly observed, monitored, and documented by serial otoscopy that is routinely done by an otolaryngologist. The opportunity to correlate the different clinical presentations of TBOM with knowledge of pathogenesis at each stage of the disease process, to discover better ways of carrying out the diagnostic tests, to choose the proper therapeutic intervention, and to evaluate the treatment outcomes were all made possible by this simple procedure that was carried out in a research environment setting. Such has profound implications regarding the need to discover more unknown aspects of the disease, to develop new therapeutic and control strategies, and to provide directions for further research.

Limitations of the Study

Since the included study participants were derived from private patients seen in a tertiary hospital and do not represent those in the general population, a study carried out in a public hospital enrolling more samples will verify our findings and probably widen our perspective about the disease, particularly about risk factors that may help clinicians heighten their index of suspicion for the possible presence of TB infection among otitis media patients. Since positive finding on PCR TB connotes only latent tuberculosis and not active disease, a study including TB culture may provide answer to the question as to whether the presence of positive PCR test is a mere contamination or an active infectious process. Post-treatment audiometric results taken from larger number of samples tested at fixed time periods, possibly categorized as short, medium and long term, will provide more conclusive results on effects of treatment interventions. Studies with better methodology may provide conclusions regarding the clinical differences between otitis media patients with TB infection and those without.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

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