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MAJOR ARTICLE

Subsequent Antituberculous Treatment May Not Be Mandatory Among Surgically Resected Culture-Negative Pulmonary Granulomas: A Retrospective Nationwide Multicenter Cohort Study

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Background. Histologic diagnosis of granuloma is often considered clinically equivalent to a definite diagnosis of pulmonary tuberculosis (TB) in endemic areas. Optimal management of surgically resected granulomatous inflammation in lung with negative mycobacterial culture results, however, remains unclear.

Methods. From 7 medical institutions in northern, middle, and southern Taiwan between January 2010 and December 2018, patients whose surgically resected pulmonary nodule(s) had histological features suggestive of TB but negative microbiological study results and who received no subsequent anti-TB treatment were identified retrospectively. All patients were followed up for 2 years until death or active TB disease was diagnosed.

Results. A total of 116 patients were enrolled during the study period. Among them, 61 patients (52.6%) were clinically asymptomatic, and 36 (31.0%) patients were immunocompromised. Solitary pulmonary nodule accounted for 44 (39.6%) of all cases. The lung nodules were removed by wedge resection in 95 (81.9%), lobectomy in 17 (14.7%), and segmentectomy in 4 (3.4%) patients. The most common histological feature was granulomatous inflammation (n = 116 [100%]), followed by caseous necrosis (n = 39 [33.6%]). During follow-up (218.4 patient-years), none of the patients developed active TB.

Conclusions. In patients with surgically resected culture-negative pulmonary granulomas, the incidence rate of subsequent active TB is low. Watchful monitoring along with regular clinical, radiological, and microbiological follow-up, instead of routine anti-TB treatment, may also be a reasonable option.

Keywords. acid-fast stain; caseous necrosis; granulomatous inflammation; pulmonary nodule; tuberculosis.

With the widespread use of chest computed tomography (CT), solitary pulmonary nodules (SPNs) and multiple pulmonary nodules are now frequently encountered in clinical setting. The underlying etiologies can be diverse and may vary with the nodular sizes, pattern, and local epidemiology [1]. In early reports, malignancy accounted for 10%–70% of SPNs [2, 3]. Nonetheless, recent lung cancer screening studies of smokers suggested that most pulmonary nodules detected on CT were benign [4, 5]. In 1 recent study of 2 separate low-dose-CT screening cohorts, for instance, the proportion of benign diseases among patients with nodules was 94.5% and 96.3%, respectively [4]. Surgical resection, however, was still performed among many patients to obtain a definite diagnosis of lung nodules [1, 6]. In approximately 25% of the surgical procedures, the resected pulmonary nodules were benign in diagnosis [4]. Furthermore, about 80% of all benign nodules were infectious granulomas [1, 6].

Granulomatous inflammation, a unique type of chronic inflammation, results from tissue reaction following cell injury

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due to various conditions [7]. Histologic diagnosis of granuloma is often considered as equivalent to a definite diagnosis of tuberculosis (TB) in endemic areas even when there is lack of TB bacteriological evidence [8–10]. Nevertheless, granulomatous inflammation is not specific to active TB. Atypical mycobacteria, coccidioidomycosis, and histoplasmosis can also be the culprit pathogen [1], and granulomatous inflammation can also result from various conditions such as autoimmune diseases, toxins, drugs, and neoplasms [7, 11]. Although necrotizing granulomatous inflammation is more likely to contain organisms, the etiology still could not be identified in 25%–40% of resected necrotizing granulomas after clinical, serological, and microbiological surveillance [12–14]. On the other hand, nonnecrotizing granuloma also does not readily exclude infectious disease as etiology [7].

Currently, most patients with surgically resected solitary pulmonary granuloma would receive anti-TB treatment after operation [10]. Adverse effects, however, could develop in as much as 53%–61% of patients who received treatment [10, 15]. Furthermore, the TB reactivation rate was low among patients who did not receive anti-TB treatment [9, 10, 15–18], and risk of active TB was similar regardless of receiving anti-TB treatment or not [15]. Nevertheless, in the above studies, extensive surveillance for TB including respiratory specimens (sputum, bronchoalveolar lavage, and tissue) for acid-fast stain (AFS) and mycobacterial culture was not performed universally among included patients. This would lead to difficulty in interpretation of the findings and clinical implication [15, 17, 18]. With the increasing use of chest CT and identification of SPNs [19], reliable evidence regarding optimal management and the indication of anti-TB treatment after surgical resection is in great need.

To evaluate the outcome of untreated pulmonary nodules after surgical resection with histological evidence of TB infection and negative culture results, we conducted this nationwide multicenter retrospective cohort study to investigate the incidence for the development of active TB in this population.

METHODS

Study Population

Between 1 January 2010 and 31 December 2018, patients with pulmonary nodule(s) who received surgical resection at 7 medical institutions with a total of >7000 beds in northern, middle, and southern Taiwan (National Taiwan University Hospital [NTUH], Taichung Veterans General Hospital [VGHTC], Kaohsiung Medical University Hospital [KMUH], Changhua Christian Hospital [CCH], and their 3 branch hospitals) and met the following criteria (1) caseous necrosis, or granulomatous inflammation in the histological samples; (2) not receiving anti-TB treatment during or within 3 weeks after the surgery were included. The institutional review boards (IRBs) of each of the above institutions approved the study (NTUH IRB No. 202001021RINB; KMUH IRB-E(I)-20200117; CCH IRB No. 200126; VGHTC IRB No. CE20127A). IRBs waived the need for informed consent as data utilized in this retrospective study have been de-identified.

Patients were excluded if (1) *Mycobacterium tuberculosis* or nontuberculous mycobacteria (NTM) were isolated within 60 days before or after surgical resection; (2) tissue culture of the pulmonary nodule was not performed; or (3) there was histological or culture evidence (such as sputum or bronchoalveolar lavage) of fungal, viral, or parasitic infection.

Per the guidelines of the World Health Organization, the standard regimen used for treating new TB cases in Taiwan consists of isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampicin plus ethambutol for 4 months if susceptibility testing is not available [20–23].

Data Collection

Information regarding patient age, sex, underlying diseases, past medical history of TB, surgical procedures (wedge resection, segmentectomy, or lobectomy), histology, laboratory test results at the beginning of tissue diagnosis, and other associated symptoms was retrieved retrospectively from medical records.

Microbiological data included AFS results from respiratory specimens and histology; mycobacterial culture results of sputum, bronchial washing, bronchoalveolar lavage, and tissue specimens were also retrieved.

Chest images (chest CT preferred) before surgical procedure were recorded, including presence of solitary or multiple pulmonary nodules, fibrocalcified lesions, bronchiectasis, cavitation, ground glass opacities, and maximum size of lesions.

Mycobacterial Culture Methods

All respiratory specimens sent for mycobacterial culture were processed as previously described [24, 25]. In brief, the specimens for acid-fast bacilli smears were processed with auramine-rhodamine fluorochrome and examined using standard procedures. Kinyoun stain method was used to confirm fluorochrome stain–positive smears. The standard *N*-acetyl-L-cysteine and sodium hydroxide method was used for the process of mycobacterial cultures. Cultures were performed by inoculating 0.5 mL of the processed specimens into Middlebrook 7H11 selective agar (Remel, Lexena, Kansas) and MGIT 960 culture tubes (BACTEC Mycobacteria Growth Indicator Tube 960 System, Becton-Dickinson Diagnostic Instrument Systems, Sparks, Maryland) [24, 25].

Follow-up and Outcome

All patients were followed up for 2 years, or until death or a diagnosis of active TB. According to the policy and regulation of the National Tuberculosis Program of Taiwan, report of all culture-confirmed TB or clinically suspicious TB cases to the

Taiwan Centers for Disease Control (CDC) is mandatory [20]. TB culture results and follow-up outcomes were obtained from the database of the 7 institutions and confirmed by obtaining information on the TB registration databases of the Taiwan CDC.

Statistical Analysis

All statistical analyses were performed using IBM SPSS software (version 23.0; SPSS Inc, Chicago, Illinois).

RESULTS

Selection of Study Participants

Figure 1 shows the process of patient identification and enrollment process. From January 2010 to December 2018, cases with histological evidence of caseous necrosis or granulomatous inflammation and negative tissue culture results who did not receive anti-TB therapy were retrieved for further analysis. All cases with positive tissue culture results for mycobacteria, fungi, or positive culture from other samples within 3 months were excluded.

Clinical Characteristics of Included Patients

In total, 116 patients were included for analysis (Figure 1). The median follow-up duration was 730 days (interquartile range: 0 day, quartile 1: 730 days, quartile 3: 730 days) since resection. Among them, 87.1% (n = 101) of subjects were followed for 2 years.

Table 1 summarizes the clinical characteristics of the included 116 cases. The median age was 58 years, with a female:male ratio of 1:1. The most common comorbidity was malignancy (n = 29 [25.0%]), followed by diabetes mellitus (n = 27 [23.3%]). Twenty-one (18.1%) cases had a medical history of TB. Among patients with malignancy, 17 of 116 (14.7%) had lung cancer and 16 of 29 (55.1%) received systemic therapy after pulmonary nodule resection. There were neither human immunodeficiency virus–positive cases nor patients receiving biologic agent in our cohort.

Fifteen (12.9%) patients did not have complete clinical follow-up for 2 years in our hospitals and among them, no active TB development was found in the following 2 years based on national TB registry.

Sixty-one patients (52.6%) were clinically asymptomatic, and they received CT either due to lung cancer screening or incidental abnormal chest radiographic findings. In the other 55 symptomatic patients, 44 (80%) patients had cough symptoms and 15 (27.2%) had dyspnea. Because the symptoms were considered due to underlying comorbidities, the 55 cases did not receive anti-TB treatment. Additionally, none of our included patients received anti-TB treatment within 6 months prior to surgery or during the follow-up period.

Surgical Procedures and Histological Characteristics of SPN

Of the 116 cases, 95 (81.9%) received wedge resection, 17 (14.7%) received lobectomy, and 4 (3.4%) received segmentectomy. Among patients with multiple pulmonary

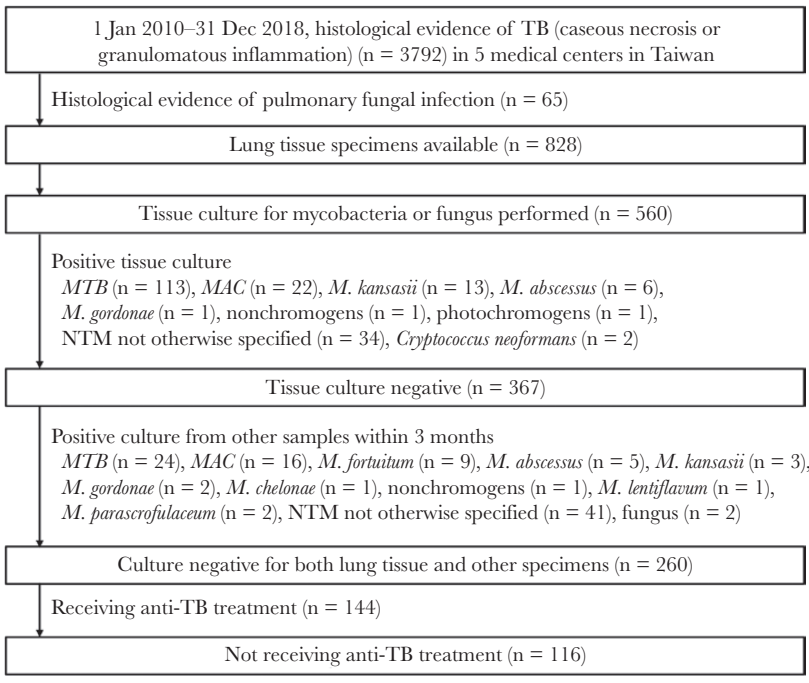

Figure 1. Case selection process. Abbreviations: MAC, *Mycobacterium avium-intracellulare* complex; MTB, *Mycobacterium tuberculosis*; NTM, nontuberculous mycobacteria; TB, tuberculosis.

Table 1. Clinical Characteristics of Study Participants (N = 116)

Variable	No. (%)
Male sex	58 (50.0)
Age, y, median (min–max)	58 (22–82)
Follow-up duration, d, median (min–max)	730 (18–730)
Surgical procedure	
Wedge	95 (81.9)
Segmentectomy	4 (3.4)
Lobectomy	17 (14.7)
Lymph node sampling	58 (50.0)
Histology	
Granulomatous inflammation	116 (100.0)
Caseous necrosis	39 (33.6)
Acid-fast staining	
Not performed	37 (31.9)
Negative	72 (62.1)
Positive	7 (6.0)
Lymph node involvement[a]	15 (12.9)
PAS or GMS stain	
Not performed	24 (20.7)
Negative	92 (79.3)
Concomitant malignancy	14 (12.1)
Underlying disease	
Malignancy	29 (25.0)
Lung cancer	17 (14.7)
Others	12 (10.3)
Status	
Remission	13 (11.2)
Under systemic treatment	16 (13.8)
Diabetes mellitus	27 (23.3)
History of tuberculosis	21 (18.1)
Chronic kidney disease stage ≥3	14 (12.1)
Cirrhosis of liver	2 (1.7)
Transplant recipients	2 (1.7)
Alcoholism	3 (2.6)
Autoimmune disease	11 (9.5)
Symptoms	
Cough	44 (37.9)
Sputum	24 (20.7)
Dyspnea	15 (12.9)
Hemoptysis	7 (6.0)
Fever	6 (5.2)
Weight loss	16 (13.8)
Clinically asymptomatic	61 (52.6)
Development of active TB within 2 y	0

Data are expressed as No. (%) unless otherwise indicated.

Abbreviations: GMS, Gomori methenamine silver; PAS, periodic acid-Schiff; TB, tuberculosis.

[a]Lymph node involvement refers to concomitant histological evidence of caseous necrosis or granulomatous inflammation of lymph nodes in addition to pulmonary nodule(s).

nodules, the granulomatous nodules in the same lung segment were removed at the same time during surgery. Otherwise, whether all lung nodules were removed during surgery depended on lung function reserve and complexity of surgical procedure. Fourteen cases (12.1%) had concomitant malignancy and granulomatous inflammation in histological specimen. The most common histological feature was granulomatous

Table 2. Radiographic Pattern and Laboratory Data of All Participants (N = 116)

Variable	No. (%)
Findings on chest CT	
Multiple nodules	64 (57.7)
Solitary nodule	44 (39.6)
Lesion size >3 cm	10 (9.0)
Associated findings	
Ground glass opacity	36 (32.4)
Fibrosis	24 (21.6)
Calcification	17 (15.3)
Bronchiectasis	13 (11.7)
Cavitation	7 (6.3)
Laboratory data, mean ± SD	
Albumin, g/dL	4.1 ± 0.6
Hemoglobin, mg/dL	13.1 ± 1.9
Leukocyte count, K/μL	6.8 ± 2.2
Segment, %	63.3 ± 11.6
Lymphocytes, %	24.7 ± 10.8
C-reactive protein, mg/dL	3.2 ± 7.8

Data are expressed as No. (%) unless otherwise indicated.Abbreviations: CT, computed tomography; SD, standard deviation.

inflammation (n = 116 [100%]), followed by caseous necrosis (n = 39 [33.6%]). In 21 cases with past history of TB, 9 had histological finding of caseous necrosis. Fifteen cases (12.9%) had concomitant histological evidence of caseous necrosis or granulomatous inflammation of lymph nodes in addition to pulmonary nodule(s). Tissue AFS showed positive results in 7 (6%) patients. Of them, 5 had past medical history of TB. Fungal stain (periodic acid-Schiff or GMS stain) was performed in 92 (79.3%) of all cases, all of which yielded negative results.

Radiographic Features of SPNs

Table 2 shows laboratory data and radiographic features of the cohort. In summary, most patients had normal hemogram and albumin values. SPNs (Figure 2A) accounted for 44 (39.6%) of all cases, whereas multiple pulmonary nodules (Figure 2B) accounted for 64 (57.7%) cases. Ten (22.7%) cases had at least 1 lesion size >3 cm in diameter (Figure 2C). All 7 (6.3%) cases with cavitary lesions had multiple pulmonary nodules.

Outcome After Observation Without Anti-TB Treatment

During a total of 218.4 patient-years of follow-up, none of the patients developed active TB according to the medical records and the data in the TB registration databases of Taiwan CDC. One 67-year-old male patient died at day 18 after surgery due to septic shock. The pathological report showed negative results of acid-fast staining and fungal staining. Cultures from sputum, bronchoalveolar lavage, and surgical specimens all showed no evidence of mycobacterial infection. In 36 cases with immunocompromised status (cirrhosis, diabetes mellitus, transplant recipients, autoimmune diseases), none developed active TB within a total follow-up of 66.6 patient-years.

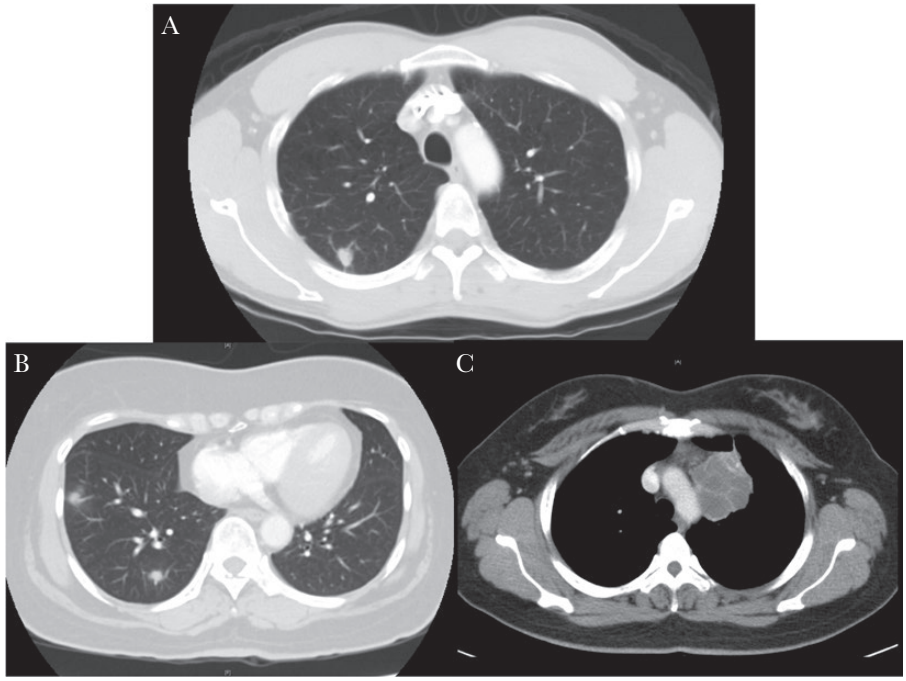

Figure 2. Chest computed tomography: a 35-year-old man with an ovoid 1.7-cm nodule with pleural tagging at the posterior aspect of the right upper lobe (*A*); a 52-year-old woman with 2 round nodules in the right lower lobe (*B*); and a 36-year-old woman with one 6.2-cm lobulated mass-like lesion in the left upper lobe (*C*).

DISCUSSION

This study investigated the incidence of active TB within 2 years in patients with culture-negative surgically resected pulmonary granulomas after thorough clinical, radiological, and microbiological workup. Mycobacterial culture was performed in all resected pulmonary granulomas with negative findings. While patients in this study may be considered to be not at high risk for TB by their physicians, the fact that no active TB developed in this cohort during a total of 218.4 patient-years follow-up implies that the risk of TB in this special group is likely to be lower than TB contacts who are test-positive by IGRA (5% in the first 2 years) [26]. Routine treatment with anti-TB drugs immediately for cases with histological evidence suggestive of TB but negative culture results should not be considered the only and standard option.

A literature review of patients with resected lung nodules having histological findings suggestive of TB yet subsequently not receiving anti-TB treatment was summarized in Table 3 [9, 10, 12, 15–18, 27]. Four hundred twenty-one cases with "tuberculoma," "granuloma," or "granulomatous inflammation" were identified in 7 studies. Of them, 212 (50.4%) cases received no anti-TB therapy. The duration of follow-up in these studies varied from 0.1 to 16.7 years. Although some data were unavailable in these studies, only 1 cancer patient who underwent regular chemotherapy developed TB reactivation [15]. In the other report, 2 cases with resected pulmonary necrotizing granulomas developed new lung nodules but did not receive additional treatment or develop new symptomatic disease [12]. Overall, the estimated incidence of active TB among patients who received no anti-TB treatment in the 7 studies was <1 per 647.2 patient-years (Table 3).

Benefit of empiric anti-TB treatment should be weighed with risk of treatment-related drug toxicity. In 1 retrospective study from Taiwan, 53% of patients with culture-negative granulomas developed adverse events after empiric anti-TB treatment and 18% of them had drug-induced hepatotoxicity [15]. In our cohort, 49.1% of enrolled cases were >60 years old and concern exists regarding the impact of age and comorbidity on management and follow-up of pulmonary nodules [28]. Considering higher risk of serious adverse effects among elderly patients [29] and uncertainty of TB diagnosis, the necessity of empiric anti-TB treatment should be carefully evaluated in culture-negative granuloma patients with low possibility of infectiousness.

In 1 large retrospective study, despite increasing use of chest CT and identifying of incidental SPNs, the incidence of lung cancer diagnosis within 2 years of SPN detection was not increased [19]. Therefore, more frequent SPN identification was presumed to be secondary to indolent infections, granulomas, and scar formation [19]. With the increasing encountering of pulmonary granulomas in clinical practice, skepticism regarding the need for treatment is warranted.

According to previous reports, infectious granuloma, such as actinomycetes, mycobacteria, fungi, and helminths infection, accounted for about 80% of benign nodules [1, 6, 13, 30]. Nevertheless, no micro-organisms can be identified after

Table 3. Literature Review of Clinical Characteristics and Outcomes of Patients With Resected Lung Nodules Having Histological Findings Suggestive of Tuberculosis Yet Subsequently Not Receiving Antituberculosis

Study, First Author, Year [Ref.]	No. of Patients, Total/No ATT	Age, y[a]	Median FU Year (Range)	No. of Patients With AFS, Positive/Performed	Coexistence of Cancer, No. (%)	No. of Patients Developing Active TB (FU Duration[b])
Ishida, 1992 [18]	36/8	53.5 (23–76)	(1–16)	16/NA	NA	0 (≥8 PY)
Mukhopadhyay, 2013 [12]	52/36	55 ± 14.9	7 (0.1–16.7)	0/52	NA	0 (217 PY)[c]
Yakar, 2016 [17]	48/37	63 (40–76)	≥2	0/25	48 (100%)	0 (≥74 PY)
Dagaonkar, 2017 [16]	19/18	63 (40–84)	1.3 (0.1–4.3)	0/19	19 (100%)	0 (23.4 PY)
Watanabe, 2017 [10]	8/3	59 (32–74)	NA	NA	1	0 (NA)
Chung, 2018 [15]	107/67	57 (21–91)	4 (0.5–4)	0/107	18 (17%)	1 (251.2 PY)
Wang, 2020 [9]	98/32	50.0 ± 13.2	2.3 (0.8–5.8)	59/98	NA	0 (73.6 PY)
Overall	421/212	NA	NA	59/301	NA	1 (≥647.2 PY)

Abbreviations: AFS, acid-fast staining; ATT, antituberculosis treatment; FU, follow-up; NA, not available; PY, person-years; TB, tuberculosis.

[a]Data are expressed as median (min–max) or mean ± standard deviation.

[b]Median number of follow-up years was assumed as mean number for calculation of incidence rate of active TB in References 9, 12, and 16. Minimum follow-up year was used for calculation in References 17 and 18. The exact follow-up period was available in the text in reference 15. Reference 10 was not included for calculation due to insufficient information.

[c]Follow-up period was available in 31 of 36 no ATT patients.

Ziehl-Neelsen and GMS stains in more than one-fourth of patients who underwent resection of radiographically solitary pulmonary granuloma [14]. In a multinational study investigating 500 histological specimens containing pulmonary granulomas [31], 42% had no identifiable etiology. Of the 58% cases with identified etiology, sarcoidosis was the most common (27%), followed by mycobacterial or fungal infections (25%). Interestingly, mycobacteria were more commonly identified outside the United States, whereas fungi were more commonly in the United States [31]. Although incidence of tuberculomas and NTM pulmonary nodules had not been established, tuberculoma is still first considered for culture-negative granuloma in TB-endemic areas. In 2019, 8732 new TB cases were reported in in Taiwan and the overall incidence of TB was 37 cases per 100 000 population [32]. Of them, 20% were sputum smear-negative and culture-negative TB [33]. Tissue biopsy or resection may, therefore, be necessary for establishing diagnosis when noninvasive testing could not confirm the diagnosis.

Histological studies and microbiological cultures are complementary, although many cases can be tested positive for both modalities. In 1 report, cultures yielded more positive results in mycobacterial infections, yet fungi were identified in most histological specimens of fungal infections [31]. These results highlight the necessity to submit biopsied tissue for cultures as well as cultures of respiratory specimens whenever feasible. In our cohort, 191 cases with pulmonary granulomas were culture-positive for mycobacteria, while 65 cases with pulmonary granulomas were diagnosed as fungal infection histologically (Figure 1). This finding again emphasizes the importance of concomitant culture and pathology surveillance to increase diagnostic yield [31]. In a study of pulmonary necrotizing granulomas of unknown cause, a careful review of clinical features, radiographic studies, cultures, fungal serologies, and special stains could lead to identification of definite etiology in 60% of all histologically unexplained cases [12].

Our study still has limitations. First, since our study design was retrospective, whether anti-TB treatment could further lower the risk of TB reactivation in culture-negative granulomas remained unknown. The effect of anti-TB treatment on TB reactivation in this special clinical entity, however, can be trivial, as the results of our previous study suggested [15]. In addition, our untreated patients might not be considered high risk to have TB by their medical doctors, which might lead to selection bias. Second, this study did not have positron emission tomography (PET) scan results. Although PET scan is promising in helping differential diagnosis of lung nodules [34], it is still unable to reliably differentiate between active TB, inactive granuloma, and malignancy [10, 35]. Besides, workup for sarcoidosis was not universal and mandatory for all patients. None of our patients, however, were diagnosed with sarcoidosis during follow-up. Finally, nucleic acid amplification testing of histopathology was not routinely used in current study. Furthermore, neither the results of tuberculin skin testing nor interferon-γ release assay (IGRA) were available since these tests are not recommended as diagnostic in this setting due to the high background rate of bacillus Calmette-Guérin (BCG, an attenuated *Mycobacterium bovis*) vaccine and the high cost of IGRAs in Taiwan [20, 36, 37].

In conclusion, after obtaining negative results through detailed clinical, radiological, microbiological, and histopathologic review, watchful monitoring instead of immediate anti-TB treatment may be a reasonable option. Regular radiographic examinations and microbiological study, however, are still warranted.

Notes

Author contributions. M.-R. L. is the guarantor of the paper and takes responsibility for the content of the manuscript, including the data and analysis. C.-L. C., with M.-R. L. and J.-Y. W., drafted the manuscript and designed the study. C.-L. C., M.-R. L., W.-C. H., H.-L. H., and J.-Y. W. were involved in data processing. C.-L. C., C.-S. C., M.-H. C., S.-H. L., and J.-Y. W. performed statistical analysis. J.-Y. W., C.-H. L., I.-W. C., J.-Y. S., and

C.-J. Y. supervised the research and provided critical revision of the article. All authors reviewed, provided input, and approved the final manuscript.

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