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The contribution of histopathology to the diagnosis of tuberculosis. Lessons from archival biopsy samples

CRISTIÁN CARRASCO[a], ALBERTO FICA[b,c], CAROLA OSORIO[d], CARLOS MUÑOZ[c], FELIPE OLIVARES[c], MARITZA NAVARRETE[e]

Background: *Histopathological analysis of tissue samples is an ancillary complementary diagnostic tool in tuberculosis (TB) with variable sensitivity and specificity according to different clinical settings. We evaluated the spectrum of histological findings, their diagnostic sensitivity, diagnostic utility, and requests over time in a sample of archival biopsies.* ***Methods:*** *Analysis of biopsies of confirmed TB cases between years 2011-2019 at a reference hospital in Chile.* ***Results:*** *The series included patients with a histological study for TB confirmed by culture (88.9%) or PCR (11.1%). In total, 34 samples were available for analysis, most of them of extrapulmonary origin (82.4%). Biopsies were taken before the start of treatment in 26 cases (76.5%) or after the start-end of treatment for different reasons in 8 cases (23.5%). Restricting the analysis to the group with pretreatment biopsies, the prevalence/diagnostic sensitivity of granulomas was 93.3%, 69.2% for caseous necrosis, 26.9% for granulomas with caseous necrosis without acid-fast bacilli (AFB), and 46.2% for AFB in any histological context. A histological score was constructed to evaluate the homogeneity of lesions, observing that 76.9% had at least four of the six components of the score. The request for biopsies was maintained over time despite the increase in the use of molecular techniques. The presence of AFB contributed to the diagnosis before microbiological results in 23.1% of the cases.* ***Conclusions:*** *Histological study continues to contribute to the diagnosis of TB, especially in extrapulmonary forms.*

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Keywords*: Diagnosis; Giant Cells, Langhans; Granuloma; Histology; Tuberculosis.*

[a]Servicio de Anatomía Patológica, Hospital Base de Valdivia, Chile
[b]Instituto de Medicina, Facultad de Medicina, Universidad Austral de Chile, Valdivia, Chile
[c]Servicio de Medicina, Hospital Base de Valdivia, Chile
[d]Laboratorio de Tuberculosis, Hospital Base de Valdivia, Chile
[e]Laboratorio de Biología Molecular, Hospital Base de Valdivia, Chile

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Correspondencia a:
Dr. Alberto Fica
Servicio de Medicina, Hospital Base de Valdivia, Bueras 1003, Valdivia, Chile
albertoficacubillos@gmail.com

La contribución de la histopatología al diagnóstico de la tuberculosis. Lecciones de muestras de biopsias de archivo

El análisis histopatológico de muestras de tejidos es una metodología antigua y auxiliar para el diagnóstico de tuberculosis (TB) con sensibilidad y especificidad variable de acuerdo al escenario clínico. Evaluamos el espectro de los hallazgos histológicos, su sensibilidad diagnóstica, su utilidad diagnóstica y cambios de solicitud en el tiempo. ***Métodos:*** *Análisis de biopsias de casos de TB confirmados entre los años 2011-2019 en un hospital de referencia en Chile.* ***Resultados:*** *La serie incluye pacientes con estudio histológico por TB confirmados por cultivo (88,9%) o PCR (11,1%). En total se contó con 34 muestras para análisis, en su mayoría de origen extrapulmonar (82,4%). Las biopsias fueron tomadas antes*

del inicio del tratamiento en 26 casos (76,5%) o luego del inicio o al finalizar el tratamiento por diferentes razones en 8 casos (23,5%). Restringiendo el análisis al grupo con biopsias pretratamiento, la prevalencia/sensibilidad diagnóstica de granulomas fue de 93,3%, de necrosis caseosa 69,2%, de granulomas con necrosis caseosa sin bacilos ácido-alcohol resistentes (BAAR) de 26,9% y de BAAR en cualquier contexto histológico de 46,2%. Se construyó un score histológico para ver homogeneidad de lesiones, observando que el 76,9% tenía al menos 4 de los 6 componentes del score. La solicitud de biopsias se mantuvo en el tiempo a pesar del incremento de técnicas moleculares. La presencia de BAAR contribuyó al diagnóstico antes que los resultados microbiológicos en el 23,1% de los casos. ***Conclusiones:*** *El estudio histológico sigue contribuyendo al diagnóstico, especialmente en las formas extrapulmonares de TB.*

Palabras clave*: Células Gigantes de Langhans; Diagnóstico; Granuloma; Histología; Tuberculosis.*

Confirmation of tuberculosis (TB) is made by a positive culture for *Mycobacterium tuberculosis* or a positive PCR result for this microorganism. The detection of acid-fast bacilli (AFB) in different biological samples has a high specificity but can be limited in cases of infections by atypical Mycobacteria or *M. leprae*. However, in an appropriate clinical context, the detection of AFB has a high predictive value to indicate a case of TB. The contribution of the histological study was historically important, especially in extrapulmonary forms of TB where the finding of granulomas with caseous necrosis, giant Langhans cells (GLC) and especially AFB in complementary stains suggested the diagnosis. However, the sensitivity and specificity of the histological findings is not optimal due to the existence of incomplete patterns, the possibility of other granulomatous pathologies, loss of a characteristic pattern in cases of HIV co-infection and the infrequent presence of AFB in tissue samples. Although histopathological patterns are still used as a proof of TB (1,2), the arrival of highly-specific and rapid molecular techniques besides cultures in liquid media with an accelerated turnaround time, could have relegated the contribution of biopsies to TB diagnosis.

Archival samples of microbiologically confirmed TB cases may allow to explore if molecular techniques have displaced this ancillary histopathological method and also evaluate the sensitivity and prevalence of specific biopsy findings (granulomas, their components, and presence of AFB) and also analyze its real contribution to the diagnosis before microbiological results are available. Literature focusing on the sensitivity of histopathological findings in correctly confirmed TB cases is scarce as well as data on its request in recent years.

Methods

Study design and samples

Retrospective observational study using histological files of patients with TB diagnosed between 2011 and 2019 at the Valdivia Base Hospital, a reference center in the Los Ríos Region located in southern Chile. From a total of 142 TB events in 139 identified patients in this period, 27 of them had histological studies, which are part of this series. Histological studies were requested at the discretion of physicians in charge.

Histological analysis

All cases were studied with standard techniques (hematoxillin and eosin) supplemented by Ziehl-Neelsen staining. Each sample was analyzed *posthoc* by one of the authors (CC), to assess the presence of granulomas, their architecture (well organized or not), caseous necrosis or non-caseous necrosis, palisading cells, GLC, and AFB. Also, polymorphonuclear cells (PMN) in excess were considered (of importance in HIV/AIDS patients). To complement the analysis, a histological lesion score was designed to evaluate homogeneity where one point each was assigned for the presence of granulomas, well-formed granulomas, caseous necrosis, palisading cells, GLC and AFB, with a

maximum score of 6 points. This score was evaluated separately in those biopsies taken before the start of treatment and those obtained during or after treatment for different reasons (see results).

Sensitivity and contribution to the diagnosis of TB

Sensitivity calculations were made separately for granulomas, caseous necrosis, palisading cells, GCL, and AFB in the subgroup without treatment. The contribution to the diagnosis was evaluated by the existence of a histological report with the presence of AFB on a date before the first available microbiological result.

Request for histological studies over time

To explore whether the request for histological studies has changed over time we analyzed its trend during years 2011 to 2019 and compared these results with the trend of molecular studies in the same period among the total number of cases of events hospitalized for TB (n = 142). The molecular techniques used were Xpert MTB/RIF (Cepheid) or RealAccurate® Quadruplex Mycobacteria PCR Kit (PathoFinder®, Maastricht, The Netherlands).

Ethical issues

This work was approved by the Scientific Ethics Committee of the Los Ríos Regional Health Service.

Results

The series is made up of 27 patients hospitalized with TB and who had histological studies, all of them identified between 2011 and 2019 with a median age of 50 years (interquartile range 39-62 years) and with male predominance (Table 1). Most patients had disseminated TB (40.7%). Almost all patients had TB confirmed by cultures (88.9%) and the rest by PCR (Table 2). Two patients had HIV/AIDS with < 200 CD4 lymphocytes/mL. There were no corticosteroids users among those studied with biopsies.

The histological archive included single or multiple samples from the same patient from different sources, totaling 34 pieces for analysis (Table 2). Multiple samples were obtained at variable periods (3 years in 2 cases with genitourinary

Table 1. General features of 27 patients admitted by TB and studied with biopsies at different sites before or after starting treatment. Hospital Base de Valdivia, Chile, 2011-2019

Variable	Results
Median age in years (interquartil range)	50 (39-62)
Male gender n (%)	17 (63%)
HIV/AIDS	2 (7.4%)
Corticosteroid users	0 (0%)
TB site n (%)	
lung	4 (14.8%)
Lymph node	4 (14.8%)
urogenital	4 (14.8%)
pleural	3 (11.1%)
vertebral	1 (3.7%)
disseminated	11 (40.7%)
lung + other site	9 (81.8%)
One site biopsy	23 (85.2%)
Multiple site biopsies	4 (14.8%)
Cases confirmed by culture	24 (88.9%)
Cases confirmed by PCR	3 (11.1%)

Table 2. Anatomical site distribution of biopsy studies among 27 patients admitted by TB, Hospital Base de Valdivia, Chile, 2011-2019

Biopsy site	n patients (%)
Patients with biopsy at a single site	
lymph node	5 (18.5%)
pleural	5 (18.5%)
vertebral	3 (11.1%)
lung	2 (7.4%)
transbronchial	2 (7.4%)
kidney	2 (7.4%)
ileum	1 (3.7%)
larynx	1 (3.7%)
bone marrow	1 (3.7%)
bone	1 (3.7%)
Partial	23 (85.2%)
Patients with biopsies at multiple sites	
vertebral-pericardium-lymph node	1 (3.7%)
bladder-kidney*	1 (3.7%)
testicular bilateral	1 (3.7%)
Transbronchial – lymph node	1 (3.7%)
Partial	4 (14.8%)
Total	27 (100%)

*3 consecutive bladder samples plus one renal.

TB and 2 months in another 2 cases). Most of the samples were of extrapulmonary origin (28 of 34; 82.4%). Biopsies were taken before the start of treatment in 26 cases (76.5%) or after the start or at the end of treatment in 8 cases (23.5%). The underlying reasons for post-treatment biopsies were motley: ileal perforation in 1 patient, post-treatment nephrectomy in 3 cases, previous diagnosis by PCR in another anatomical site (2 cases) or clinical suspicion in the remaining 2 cases.

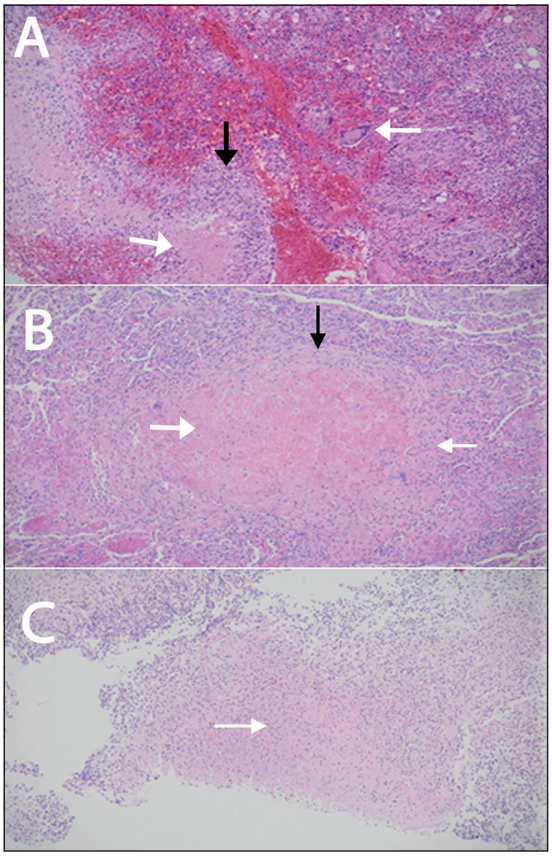

Figure 1. Examples of different histological findings among patients with TB. **A:** Granuloma with a well-organized architecture and caseous necrosis (white left arrow), palisading cells (black arrow), and Langhans giant cells (white right arrow). AFB were detected by a complementary Zielh-Neelsen stain. **B:** Microphotography of a granuloma with caseous necrosis (white left arrow) without palisading cells. In this case the granuloma is surrounded by a fibroblast layer (black arrow). A giant Langhans cell is shown (white right arrow). AFB were detected by a complementary Zielh-Neelsen stain. C: Granuloma with central necrosis and inflammatory cells but not caseum (white arrow). In this case, AFB were not detected. All samples were stained with hematoxylin-eosin and amplified at 40x.

Description of histological findings

In those patients not treated before biopsies were taken, almost all cases presented granulomas and with a well-organized architecture (Figure 1). Caseous necrosis occurred in approximately two-thirds of cases. GLC was more frequent than palisading cells (73.1% versus 61.5%, Table 3). The diagnostic sensitivity of granulomas with caseous necrosis but without AFB was low (26.9%), and higher in the case of AFB in any histological context (46.2%). Despite variations in the prevalence of a particular histological finding, homogeneity was relevant in this study. Thus, histological lesions had at least 4 of the 6 components analyzed (76.9%; granulomas, caseous necrosis, well organized architecture, palisading cells, GLC and AFB) (Figure 2).

Because in some cases the biopsies were taken after the start of treatment (8 of 34 cases; 23.5%), we compared the histological score between the group with pre- and post-treatment biopsies without finding significant differences (non-parametric Mann- Whitney test). Although the frequency of AFB observed in the treated or already treated group was lower compared to the pretreatment group (1 in 8 samples; 12.5% vs 46.2% in the pretreatment group), this difference was not significant.

Table 3. Histopathological findings among 26 biopsy samples from patients admitted with TB taken before treatment, Hospital Base de Valdivia, Chile, 2011-2019

Finding /sensitivity	n/N (%)
Granuloma	24/26 (93.3%)
Well organized granuloma	23/23 (95.8%)*
Caseous necrosis	18/26 (69.2%)
Necrosis without caseum	6/26 (23.1%)
Palisading cells	16/26 (61.5%)
Giant Langhans cells	19/26 (73.1%)
Polymorphonuclear cells in excess	5/24 (20.8%)*
AFB	12/26 (46.2%)
Granulomas with caseous necrosis but negative AFB	7/26 (26.9%)

*Calculated only among cases with granulomas.

Histological study in patients with HIV/AIDS

Two patients with this condition were included in this series; however, they did not present a similar pattern. Granulomas and caseous necrosis were detected in both. In one of them without a well-organized architecture and no excess of PMN cells and in another, the architecture was organized but with excess of PMN cells. Excess of PMN cells was also detected in non HIV/AIDS patients and reached near 20% in the whole sample (Table 3).

Trends over time

No evidence of histological requirement decay was observed. The request for biopsies was maintained over time despite the increase in the use of Xpert MTB/RIF, provided at free cost by the Ministry of Health. The use of Real Accurate PCR decreased after the increase of Xpert MTB/RIF (Figure 3). This test was acquired with local funds in our hospital and replaced when Xpert MTB/RIF arrived.

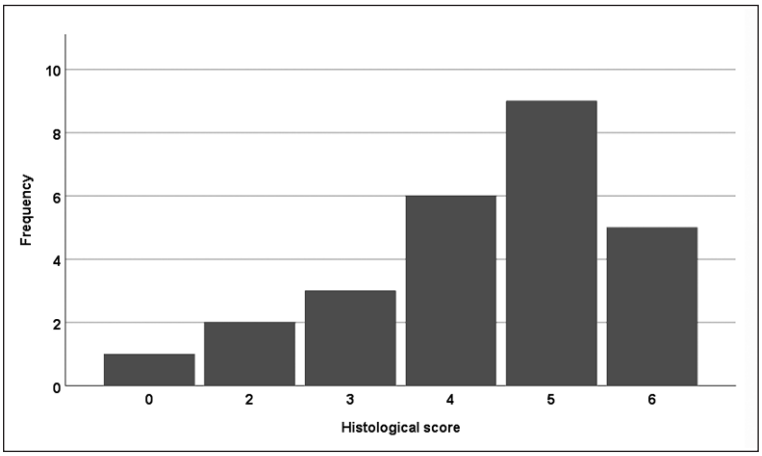

Figure 2. Distribution of the histological score among 26 biopsy samples of patients affected by TB and taken before treatment, Hospital Base de Valdivia, Chile, 2011-2019. Most patients had at least four of the following features: granuloma, organized architecture of the granuloma, necrosis with caseum, palisading cells, giant Langhans cells and AFB (one point each).

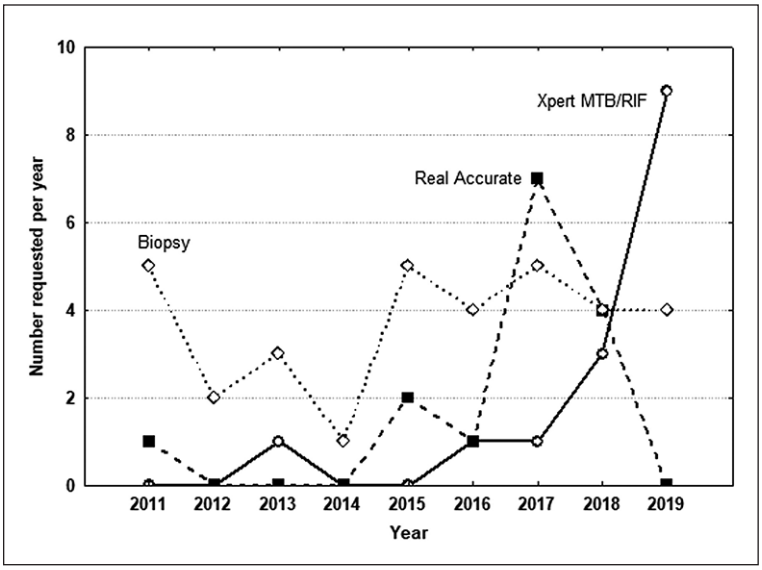

Figure 3. Trends in the use of molecular methods and/or histological study in the diagnosis of 142 events of pulmonary or extrapulmonary TB, Hospital Base de Valdivia 2011-2019. The arrival of the Xpert MTB/RIF system provided free of charge by the MINSAL increased the use of this technology (Spearman + 0.82; $p < 0.05$) and displaced other techniques such as the alternative PCR purchased by local funds. funds. Biopsy requests remained unchanged.

Contribution of the histological study to the diagnosis of TB before microbiological results

As discussed above, in 12 out of 26 patients with biopsies obtained before the start of treatment, AFB were detected in the histological samples, and in 6 of these cases, the biopsy was the first indication of the diagnosis of TB. Thus, biopsies contributed to the diagnosis in 23.1% of the cases studied by histology before treatment.

Discussion

We believe that the results of this work are relevant because they show that the histological study continues to be a significant diagnostic strategy in the recognition of TB, especially in its extrapulmonary forms, sometimes allowing an early diagnosis. In addition, we obtained a detailed diagnostic sensitivity for different histological findings. Granulomas, even without the coexistence of caseous necrosis, represent the most sensitive component to suggest the diagnosis, with GLC being the most important specific cell finding. In addition, granulomas associated to TB appear rather homogeneous in its global composition. The presence of AFB in tissue samples was not an uncommon phenomenon, reaching almost 50% of diagnostic sensitivity, a relevant issue to suggest TB in appropriate clinical settings. One advantage of this work is that involved different TB forms, not being restricted to a simple anatomical site.

Biopsies have been a central part of the study of extrapulmonary forms of TB, for instance in cutaneous, pleural, spinal, lymph node, peritoneal, intestinal, and urogenital forms[3-15], Histopathology has also been important in autopsy findings[2,16]. The search for granulomas with caseous necrosis suggests the diagnosis, ideally if it is accompanied by AFB in a compatible clinical scenario. The presence of AFB in biopsies is also possible in cases of atypical mycobacterial infections or in leprosy, so its finding is only presumptive for the diagnosis of TB and the clinical context should be considered. For example, the presence of skin lesions with focal neurological involvement suggests leprosy, and the finding of AFB in an immunosuppressed patient may indicate either *M. tuberculosis* or atypical mycobacterial infection[17,18]. The more straightforward scenario to implicate TB in tissue samples with AFB is when is associated to classical risk groups without HIV infection such as inmates, immigrants from high endemic countries, those with alcohol abuse and/or chronic liver disease, native populations, poor and homeless. Granulomas with caseous necrosis and GLC but without AFB, are also highly suggestive of TB because histoplasmosis is one the few alternatives that is dependent on a geographic exposure not observed in template climates[19]. Alternative etiologies for granulomas without AFB and caseous necrosis include atypical mycobacterias, *M. leprae*, histoplasmosis, cryptococcosis, coccidioidomycosis (usually with intense suppuration), and syphilitic gumma[19,20]. In the case of granulomas with non-caseous necrosis, options include cat scratch disease (associated with microabscesses)[21] and non-infectious causes as Crohn's disease, sarcoidosis, and some autoimmune vasculitides[22-24]. The analysis of the clinical information, epidemiological exposure and the support of laboratory tests and images, will allow the approach the definitive diagnosis.

The sensitivity reported for the detection of AFB in biopsies has been variable with values from 0 to 60% and whose presence is positively associated with the presence of granulomas[4,25-27]. The observed trend towards a lower frequency of AFB in our samples for already treated patients suggests that microbiological eradication can also be verified in biopsies.

It has been described that histological findings are not classical in patients with HIV/AIDS. Rather one may expect a disorganized architecture, with intense necrosis and numerous AFB. Lesions are rich in eosinophils and PMN cells[28]. In our series, only 2 patients had HIV/AIDS coinfection, presenting a mixed composition in the biopsies.

In this study, the histological report made it possible to advance the diagnosis in some cases and initiate the corresponding therapy. In other cases, the results were available after the microbiological report and did not have a therapeutic impact. The presence of AFB has been used systematically by others, prospectively and before the availability of molecular studies, to initiate treatment on an empirical basis in patients with AIDS[18]. We believe this can be accomplished also in patients without HIV co-infection belonging to classical risk groups and with a reasonable initial clinical exclusion of alternative etiologies. On the other hand, the absence of an immediate therapeutic impact does not invalidate the use-

fulness of the histological study since sometimes carries an unsuspected diagnostic possibility or allows its exclusion, and in others may confirm a disseminated disease. In any case, the histological study does not compete with other strategies but complements the study, being most appropriate to systematically include samples for histological, conventional microbiological and molecular studies in the procedure. In fact, it is often observed in clinical practice the omission of the microbiological study in the study of lymph node biopsies or other tissues, limiting the scope only to the possibility of cancer. Certainly, molecular tests have revolutionized detection possibilities[29], but they sometimes have imperfect sensitivity[30] and are not able to detect atypical mycobacteria unless such a possibility has been expressly included.

Our work has limitations related to the specificity of the histological findings because causes other than tuberculosis were not included, the low prevalence in the sample of patients with HIV/AIDS co-infection and the non-inclusion of molecular studies for comparative purposes. However, it sheds light on the usefulness of the histopathological study, its limitations and its contribution to diagnosis and treatment. The request for biopsies, integrated with microbiological studies, seems to be still necessary when mycobacterial infections are suspected or if other diagnostic strategies are not available or have not given relevant results. Finally, it seems necessary to standardize the histological report on biopsies with suspected tuberculosis, including all possible parameters, even if some of them are absent.

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