

Original Article

The role of TNF receptors as mediators of chronic vasculitis in possible milder forms of the CNS tuberculosis

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Abstract

Introduction: Central nervous system (CNS) tuberculosis (TB) is the most severe form of TB due to its high mortality and functional sequelae. There are several differential diagnoses for TB; and, it can also cause secondary conditions, such as vasculitis.

Methodology: 155 biopsies, corresponding to 155 different patients out of 5,386 registered biopsies from 2008-2013, met the criteria of unknown etiology vasculitis and evidence of cerebral vascular disease. These were analyzed to assess the presence of central nervous system TB. The selected cases were assessed with Suzaan Marais (SM) criteria for clinical tuberculosis. After that, Ziehl-Neelsen (ZN) staining and polymerase chain reaction (PCR) were performed to amplify a fragment of the insertion sequence IS6110 of *M. tuberculosis*. 21 patients met the criteria for definitive tuberculosis by ZN staining and PCR, and 2 met the criteria for possible tuberculosis. Tumor necrosis factor (TNF)- α , TNF-R1, and TNF-R2 were determined by immunohistochemistry in histological sections from formalin-fixed paraffin-embedded (FF-PE) tissues in the 23 selected patients.

Results: Granulomatous TB was present in almost half of the cases. TNF-R1 and TNF-R2 were expressed mainly in blood vessels, histiocytes, and macrophages.

TNF-R2 expression was higher than the other markers, which suggests an anti-inflammatory response against *M. tuberculosis*

Conclusions: The histopathological presentation of TB is not always limited to granulomas, abscesses, or meningitis; there are also clinical presentations characterized only with chronic inflammation of nervous and vascular tissue.

Key words: vasculitis; CNS tuberculosis; TNF- α ; TNF-R1; TNF-R2.

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Introduction

Tuberculosis (TB) is an infection caused by the bacilli of the *Mycobacterium tuberculosis* complex.

Until the coronavirus pandemic, TB was the infectious disease with the highest mortality, even above HIV/AIDS [1]. According to the World Health

Organization (WHO) data for 2022, there were between 24,000 and 41,000 new cases of TB in Mexico, with a rate of 25 cases per 100,000 inhabitants [2].

Pulmonary TB is the most frequent clinical presentation. However, extrapulmonary forms exist, such as pleural, miliary, nodal or central nervous system (CNS) tuberculosis. According to CENAPRECE (Centro Nacional de Programas Preventivos y Control de Enfermedades), Mexico, in 2021, CNS TB represented around 2.3% of all cases. Nevertheless, it has the highest lethality, and 30% of the survivors present functional sequelae [3,4,5].

The clinical features of CNS TB may vary depending on the anatomic affected area and the presentation form of the disease, which can be meningeal [6], parenchymal (with the presence of tuberculomas and abscesses), or Pott's syndrome [7].

TB pathogenesis is characterized by humoral changes, such as the expression of Interferon- γ (IFN- γ), Tumor Necrosis Factor α (TNF- α), and its soluble receptors (TNF-R1 and TNF-R2) as well as IL-10 [8]. Moreover, there are modifications of the nervous tissue cells and vascular structures [9], including perivascular cellular infiltration and expression of proinflammatory and anti-inflammatory mediators. TNF-R1 receptor plays an essential role in the initiation of the TNF- α dependent endothelial inflammatory response, while the TNF-R2 activates the proliferation of several immune cells, cytotoxicity, and NF- κ B activation [10].

TB diagnosis could be a challenge due to the broad spectrum of clinical features that it shares with other pathologies, even despite the additional tools that exist to diagnose it [3,11,12]. For instance, TB and autoimmune vasculitis share some clinical features, including constitutional alterations [13]. Both conditions are differentially diagnosed, even though, there are some reports of TB-associated Takayasu arteritis and cutaneous vasculitis [14]. Some causes of vasculitis such as Wegener's granulomatosis or Churg-Strauss syndrome can also cause confusion at the time of diagnosis as tuberculosis differential diagnosis. Some causes of vasculitis such as Wegener's granulomatosis or Churg-Strauss syndrome can cause confusion at the time of their approach, since they share clinical characteristics with TB [15].

This research aimed to relate the presence of *M. tuberculosis* in chronic vasculitis with a different morphological pattern than the one reported in the literature as a possible clinical milder form of CNS TB and, to determine if TNF- α possibly plays a role in this mechanism.

Methodology

Population study

A retrospective, cross-sectional, observational study was performed. Clinical data from patients treated in the Neuropathology Department of the National Institute of Neurology and Neurosurgery "Manuel Velasco Suárez" from 2008 to 2013 were analyzed. All these patients received medical and neurosurgical management. An intraoperative neural tissue sample from the affected area due to a myriad of neurological conditions was also obtained.

Selection of cases

We selected cases that met the histopathological criteria for undetermined etiology vasculitis [3,16]. For this purpose, we analyzed the neural tissue samples. The average size of the tissue samples was 4-8 cm², with 3 cut levels for each patient. As these are stereotaxic biopsies, the entire sample sent by the surgeon was included. All tissues corresponding to the selected cases were formalin-fixed paraffin-embedded (FF-PE). 3 μ m cuts were made from the biopsies and mounted in polymerized slides and heat-fixed in an oven at 75 °C for 1h. The histological sections were rehydrated through a series of solvents, including xylene and alcohol in decreasing concentration. After that, the slides were stained with Harry's hematoxylin for 15 min; excess dye was removed with acidified alcohol and rinsed with ammonia water. After this, the histological specimens were stained with eosin for 10 seconds, and dehydration of the tissue was carried out with alcohol in increasing concentration until it reached xylene concentration. Subsequently, the samples were mounted in slides with EntellanTM (MERK, Darmstadt, Germany) resin, and a coverslip was placed. The observation included all the slides derived from the histological section. The pathologist subjectively quantified inflammation in a scale from 1 to 3 as mild, moderate, and severe. The histological diagnosis of vasculitis was confirmed by the presence of inflammatory perivascular infiltrate of neutrophils, lymphocytes, macrophages, or mixed cell populations, the infiltrates needed to be associated with at least one of the following findings: dissection of the vascular layers, necrosis or hemorrhage, the latter demonstrated by the presence of erythrocytes. After that, the medical records corresponding to the samples were evaluated for Suzzan Marais criteria and were classified as definitive, probable, possible, and non-tuberculosis. The Suzaan Marais criteria is a scale that assesses central nervous system TB by clinical features, cerebral spinal fluid analysis, image findings, and the presence

of the bacilli demonstrated by acid-fast bacilli or nucleic acid amplification test. We obtained the clinical data used for each patient from medical records, and all those cases with evidence of HIV/AIDS, immunocompromised, or previously diagnosed with TB were excluded from the study.

Determination of M. tuberculosis by Ziehl-Neelsen staining and amplification of IS6110 by PCR

All FF-PE tissues were analyzed using a ZN stain. 3 µm cuts were made from the biopsies, mounted on polymerized slides, and heat-fixed in an oven at 75 °C for 1 hour. Histological sections were rehydrated through a series of solvents, including xylenes and alcohols in decreasing concentration. After that, histological specimens were placed in glass slides with carbol-fuchsin for 30 minutes. Tissue washing was carried out with acid alcohol, and the slides were stained with methylene blue dye [17].

A fragment of the IS6110 insertion sequence of *M. tuberculosis* was amplified using polymerase chain reaction (PCR) for the cases that could not be diagnosed by ZN stain. DNA was obtained from the FF-PE tissues using the phenol-chloroform technique [18,19]. The genomic DNA concentration was calculated at 100 ng/µL for each reaction. HotStarTaq Master Mix Kit from Qiagen Quality, Cat. No. 203443, Lot. No. 145034127 (San Diego, CA, USA) was used, and primers classically described [18].

Immunohistochemistry

Histological sections of FF-PE tissues were used to determine the presence of TNF-α, TNF-R1, and TNF-R2 by immunohistochemistry. The histological sections were set on poly-L-lysine (Bio SB detection system, Santa Bárbara, CA, USA) treated slides. We used a monoclonal mouse antibody for TNF-α detection (INVITROGEN, Cat. No. AHC3612, Waltham, MA, USA), a rabbit polyclonal IgG to detect TNF-R1

(GENE TEX Inc., Cat. No. GTX15567, Alton Pkwy Irvine, CA, USA) and a mouse monoclonal antibody to detect TNF-R2 (GENE TEX Inc., No Cat. GTX17038, Alton Pkwy Irvine, CA, USA).

Approval by the ethics committee

All the samples were obtained after the patients gave an informed consent letter for diagnosis and research, and data were obtained from the clinical records. The project was approved by the local ethics committee with the registry number 28/19. This research was performed according to the guidelines of the Declaration of Helsinki.

Results

Characteristics of the study sample

Out of the 5,386 registered biopsies from 2008 to 2013, 155 corresponding to 155 patients showed histopathological evidence of vasculitis of undetermined etiology, non-specific chronic inflammation, and recent or old cerebral hemorrhage. From the 155 selected biopsies, 23 accomplished the Suzaan Marais criteria, of which 21 met the study criteria for definitive TB, and 2 met the criteria for possible TB.

78.26% of the total cases were men, whereas 21.73% were women. The male/female ratio was 3.6:1. The patients had a median age of 44 years, with 30.43% in the 40–49-year age group.

Most of the cases were misdiagnosed since the medical records reported that the patients underwent neurosurgery for CNS neoplasms in 52.17% (n = 12/23). Indications for surgery included astrocytoma, cavernoma, glioblastoma, hemangioblastoma, schwannoma, and cerebral metastasis. Also, 34.77% (n = 8/23) of the patients were hospitalized for non-tuberculosis neurological infections, out of which 30.43% (n = 7/23) were diagnosed with brain abscesses and 4.34% (n = 1/23) with bacterial meningoencephalitis. Moreover, 4.34% (n = 1/23) of the cases were misdiagnosed as a single case of Arnold-Chiari disease. Remarkably, only 8.69% (n = 2/23) of the cases had a previous report of tuberculosis evidence, though none of the 23 patients were discharged with a diagnosis of tuberculosis.

The most common clinical feature was headache, which presented in 73.91% (n = 17/23), whereas 43.47% (n = 10/23) of the patients presented neuromotor alterations. Other symptoms were manifested in a smaller percentage (Table 1).

Table 1. Clinical features of the cases with definitive and possible TB.

Clinical features	Patients (n=23), %
Headache	17 (73.91)
Focal	9 (39.13)
Progressive	6 (26.08)
Neuromotor alterations	10 (43.47)
General Symptoms (nausea, emesis, asthenia, adynamia, diaphoresis)	12 (52.17)
Fever	6 (26.08)
Hyporexia	5 (21.73)
Others (seizures, cranial nerve (II, III, IV, V, VI), cognitive, vision and gait alterations)	9 (39.13)

Table 2. Morphological characteristics of tissues with tuberculosis of the central nervous system.

Localization	Lesion	% of biopsy samples
Parenchymal (n = 17/23)	Inflammation	100.00
	White matter disturbances	94.11
	Necrosis and edema	88.23
	Axonal damage, presence of foamy cells and hemorrhage evidence	70.58
	Destruction of blood vessels	52.94
	Granulomas	47.05
	Thrombosis	29.41
Meningeal (n = 6/23)	Inflammation	100.00
	Necrosis and Granulomas	50.00
	Hemorrhage	33.33
	Thrombosis	16.66

Detection of acid-fast Bacilli (AFB) in biopsies and amplification of IS6110 sequence by PCR

The ZN stain was performed for all FF-PE tissues corresponding to 155 biopsies. The definitive TB diagnosis was confirmed in eight patients (Figure 1). The rest of the samples (corresponding to 15 patients) were evaluated by the detection of the IS6110 sequence by endpoint PCR. We confirmed the diagnosis of 13 patients with definitive TB, and two remained with the diagnosis of possible TB (Figure 1).

The main parenchymal topographical areas affected by *M. tuberculosis* were the frontal lobe and the cerebellum, 47% and 17.64% respectively. Additionally, we found less frequent harm in temporal lobe, parietal lobe, occipital lobe and the brain stem. On the other hand, from the 23 samples, six had meningeal disturbances (26.08%).

Histopathological aspects of M. tuberculosis and vasculitis induced lesion

The samples from the patients with definitive TB diagnosis underwent a histopathological study.

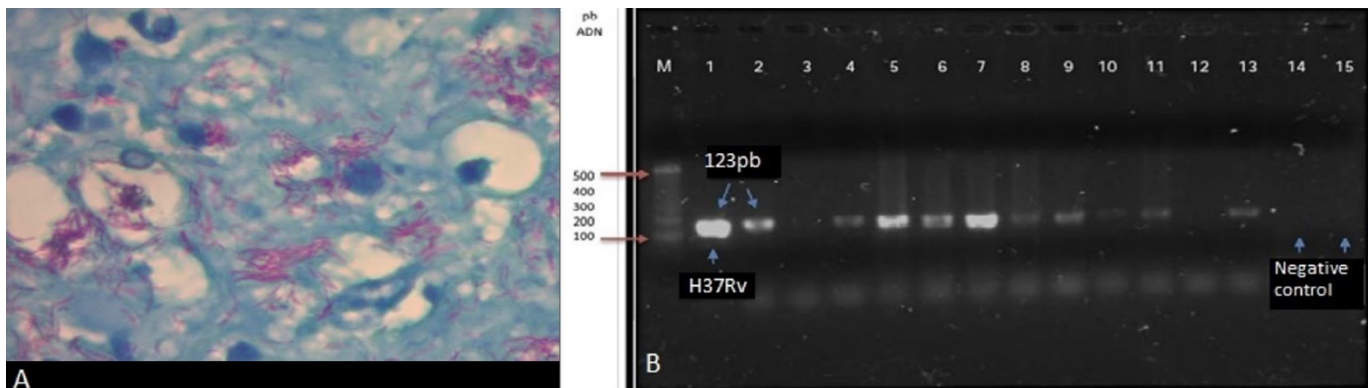
Necrosis, edema, axonal damage, and the presence of granulomas were some of the lesions found in the nervous tissue (Table 2).

Cell infiltrates were found with a higher frequency in perivascular meningeal vessels (66.66%) than in parenchymal blood vessels (17.64%). However, there was a predominance of granulomas in perivascular parenchymal sites (35.29%) compared to meningeal blood vessels (5.88%). We also found different vascular lesions that are shown in Figure 2.

Immunohistochemistry

The histopathological diagnoses of the samples were the following: chronic vasculitis in all cases, 4.34% (n = 1/23) of the cases had vasculitis accompanied by granulomatous meningitis, 8.69% (n = 2/23) combined with granulomatous encephalitis and 30.43% (n = 7/23) mixed with granulomas. The expression of TNF- α , TNF-R1, and TNF-R2 was determined in all samples, and surprisingly, the higher expression of these molecules was found in the cases where vasculitis was associated with granulomas.

Figure 1. Microbiological and molecular diagnostic tests for *M. tuberculosis*.



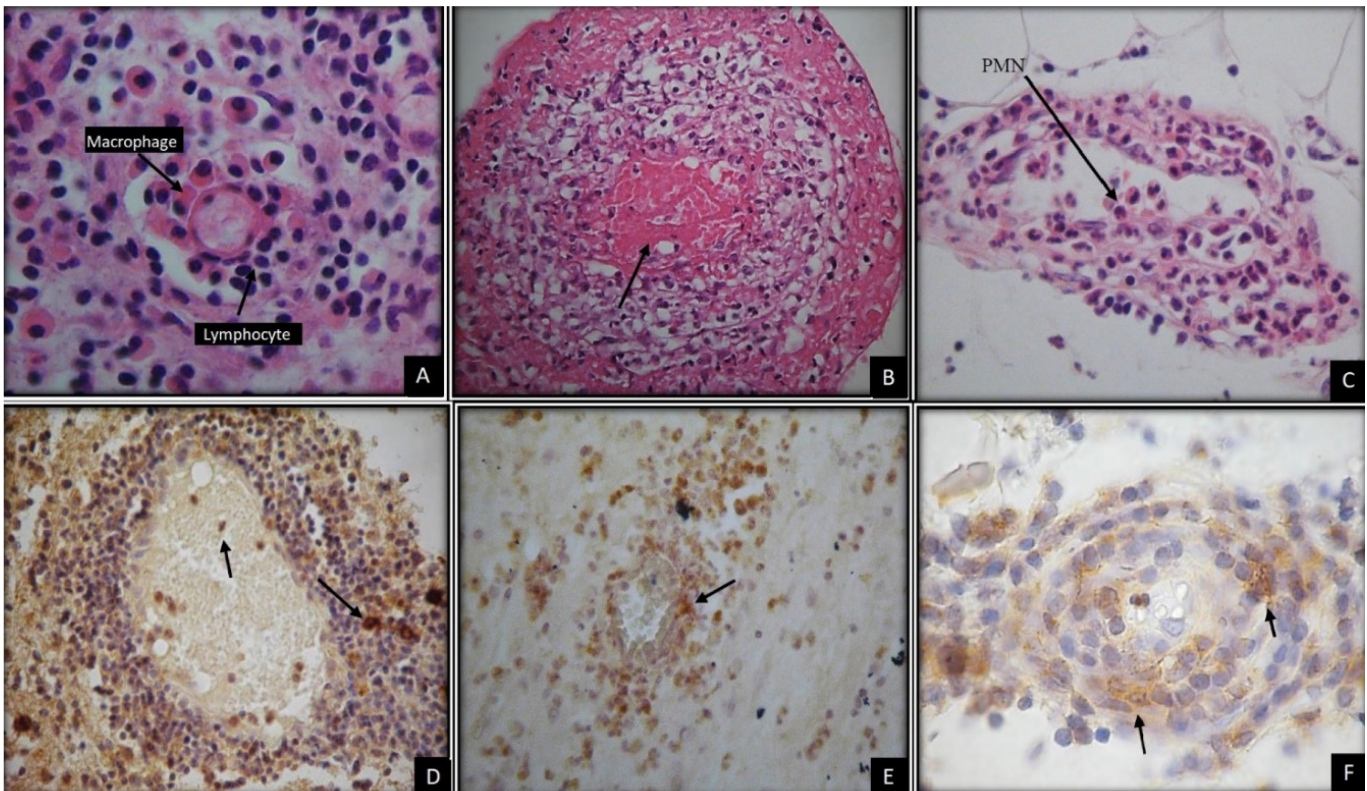
A) Microphotography of human brain tissue with Ziehl Neelsen (ZN) staining: Evidence of staining for acid-fast bacilli (AFB) (fuchsia red color) on the blue background, by methylene blue (x1000). **B)** A 2% agarose gel in which the 123 bp band corresponding to the IS6110 sequence of the *M. tuberculosis* is visible. Column M corresponds to a molecular weight size marker. Line 1 corresponds to a DNA positive control (reference strain of *M. tuberculosis*: H37Rv); lines 2, 4, 5, 6, 7, 8, 9, 11, and 13 were individuals with a positive result for *M. tuberculosis*, line 3, 10 and 12 individuals with a negative result, line 14 is negative control of mouse heart tissue and line 15 is negative reaction control.

Table 3. Expression of TNF- α , TNF-R1 and TNF-R2 in nervous tissues infected with *M. tuberculosis*.

Patient	TNF- α	TNF-R1	TNF-R2	Histopathologic diagnosis
1	PMN, BV	BV	Polycarionic histiocytes, BV	Granulomatous meningitis
2	BV	(-)	BV	Granuloma
3	BV	(-)	BV	Leukocytoclastic vasculitis
4	Histiocytes, BV	PMN, BV, MGC	Histiocytes, MGC	Granuloma
5	Histiocytes, BV	Histiocytes, BV	(-)	Lymphocytic encephalitis
6	Gesmistocytes, Astrocytes, Histiocytes, BV	Histiocytes	Histiocytes	Intraparenchymal hemorrhage
7	PMN, BV	(-)	BV	Chronic meningitis
8	BV	(-)	MØ, BV	Leukocytic meningitis
9	Histiocytes, BV	(-)	(-)	Chronic meningitis
10	(-)	(-)	MGC, Astrocytes	Severe vasculitis with thrombosis
11	BV	(-)	PMN, BV	Granuloma
12	BV	Histiocytes, MGC	Histiocytes, MØ	Granuloma
13	BV	(-)	Histiocytes	Encephalitis
14	(-)	BV	Gemistocytes	Granuloma
15	BV, PMN	BV, MØ, Gemistocytes	Histiocytes, BV	Hemorrhagic encephalitis
16	BV	(-)	Histiocytes, MGC, BV	Encephalitis with areas of infarction
17	PMN	(-)	Histiocytes, MGC	Granulomatous encephalitis
18	BV	Gemistocytes	Astrocytes, Gemistocytes, MØ, BV	Granulomatous encephalitis
19	BV	(-)	Histiocytes, BV	Granuloma
20	MØ	(-)	(-)	Vasculitis
21	Sparkling MØ, BV	(-)	(-)	Encephalitis
22	(-)	(-)	(-)	Necrotic tissue
23	MØ, BV	Polycarionic MØ	(-)	Granuloma

MØ: Macrophage; BV: Blood Vessel; MGC: Multinucleated Giant Cells; PMN: Polymorphonuclear; (-): Negative.

Figure 2. Histopathology of vascular lesions induced by *M. tuberculosis*.



A) Perivascular infiltration by macrophages and lymphocytes (x400). **B)** Total occlusion of the blood vessel by thrombus formation inside, with the destruction of elastin fibers by infiltrating of lymphocytes (x400). **C)** Vascular infiltrate by polymorphonuclear cells (x400). **D)** We found expression of TNF- α on the cellular infiltrate, especially in macrophages and polymorphonuclear (PMN) cells (x400) in the blood vessel. **E)** The TNF-R1 marker is observed on the infiltrated blood vessel (x400). **F)** Macrophages around blood vessels with mixed inflammation (lymphocytes and macrophages) expressed TNF-R2 (x400).

In all patients, the TNF-R2 was expressed mainly in blood vessels (43.47%), histiocytes (39.13%), and multinucleated giant cells (17.39%), whereas TNF-R1 was expressed in blood vessels (21.73%), histiocytes (13.04%), and gemistocytes (8.69%). The structures with the highest expression for TNF- α were blood vessels (78.26%), histiocytes (17.39%) and macrophages (13.04%). In addition, polymorphonuclear (PMN), astrocytes, and foamy cells had elevated expression of TNF- α , TNF-R1, and TNF-R2. (Table 3) (Figure 2).

Discussion

CNS TB continues to be a diagnostic challenge due to its different clinical presentations, either meningeal or parenchymal, and its considerable variability of clinical features. This study aimed to relate the presence of *M. tuberculosis* in chronic vasculitis with a different morphological pattern than the one in classical descriptions as a possible clinically milder form of CNS TB and whether TNF- α plays a role in this mechanism.

According to the literature, meningeal tuberculosis is usually confused with meningitis associated with other pathogens [20]. In addition, some authors have reported metastatic tumors located at the brain base such as schwannomas or meningiomas as the initial diagnosis in cases that afterwards were diagnosed as CNS TB [21]. Cerebral abscesses, neoplasms such as glioblastoma, and lymphomas, among others, are the primary initial diagnoses mentioned as parenchymal TB confusers [22]. In addition to this reported data, we found a single TB case misdiagnosed with Arnold Chiari's disease in our study.

The clinical features of TB depend on the type of lesion and the topographic affected area. The clinical features we found were weight loss, fever, cranial nerves alterations, dysarthria, paresis, paresthesia, and meningism. All these features have been reported in the literature as characteristics of CNS TB and its differential diagnoses [20-24]. Additionally, we found gait disorders, behavioral changes, mental function alterations, and interestingly headache as the main symptom of CNS TB, which has not been previously reported.

Tuberculous meningitis has been reported as the most frequent manifestation of CNS TB [25]; however, in our study, the parenchymal area was mostly affected.

Vasculitis induced by infectious agents can be direct, indirect, or both [26]. During the review of the literature, we only found reported cases of CNS vasculitis caused by TB. In 2018, Parent *et al.* reported

a case of CNS vasculitis induced by bacille Calmette-Guerin (BCG) immunization by isolating *Mycobacterium bovis* from urine culture in a patient with CNS angiitis symptoms [27]. They described a biopsy with chronic vascular inflammation and no necrotizing granuloma formation, but perivascular haemorrhage with a predominance of lymphocytes, plasmatic cells, and histiocytes. Our histological analysis confirms these results. In our study, we also observed thrombosis in meningeal samples. In addition, we found white matter disturbances in the parenchymal samples, including the opening of neuropil, where the neuronal extensions (dendrites and axons) were separated and had demyelinated fibers; also, alterations in the shape of the fibers, finding them twisted and with different thicknesses. Edema manifested as opening spaces that separated the tissue from the pericellular or interstitial blood vessels (Virchow-Robin spaces) that appeared white in the light microscopy field, and axonal damage manifested by changes in the histological architecture that included different thicknesses, serpiginous forms, rupture, or axonal vesicles that gave it a spongy appearance. Destruction of blood vessels, granulomas, thrombosis, histiocytes, gemistocytes, and polymorphonuclear cells were evident. This highlights that parenchymal vasculitis is even more severe than meningeal vasculitis.

Perivascular granulomas have been a critical feature in CNS vasculitis induced by TB. However, in our results more than half of the patients did not have perivascular granulomas. To sum up, we can conclude that the absence of perivascular granulomas does not dismiss the presence of CNS vasculitis by *M. tuberculosis*.

Hasegawa *et al.* determined the expression of TNF- α soluble receptors in neutrophils of patients with positive myeloperoxidase anti neutrophil cytoplasmic autoantibody (ANCA) vasculitis, finding a higher expression than in healthy subjects [28]. In another study, Gao Huan *et al.* determined the presence of ANCAs in patients with TB. Even though the measure of ANCAs was not performed in our research, it would be worth investigating an association among ANCAs positive vasculitis, TB diagnosis, and the expression of the TNF- α soluble receptors in further studies [29].

In the literature reviewed, we did not find any study reporting the expression of TNF- α receptors in CNS vasculitis induced by *M. tuberculosis*. We found a considerable expression of TNF-R2 in most cells and tissues, which has been related to inflammatory processes.

However, more extensive randomized studies should be performed to accurately determine the pathogenesis of TB-induced vasculitis, evaluating the cellular and humoral immune responses, and exploring the mechanisms for the bacilli entry to the CNS starting by doing tests on animal models [30].

Conclusions

CNS vasculitis and TB are closely related; therefore, it is crucial to consider the diagnosis of TB in patients who present clinical or radiological data compatible with vasculitis. The histopathological presentation of TB is not always limited to granulomas, abscesses, or meningitis. There are also presentations characterized by only chronic inflammation of nervous and vascular tissue. The expression of TNF-R2 was frequent in the blood vessels of patients with TB-induced CNS vasculitis, and its presence could be correlated with neuroprotection against inflammatory events that could become catastrophic.

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Authors' contributions

SLC; HPR; ARE: conceived the present research, SLC; MMJ; SGC: conceived and planned the experiments, RCA; FBMA; PDY; MCB; carried out the experiments, SLC; RLJP; supervised the finding of this research, RCA; EYLM; TSML; SGY: wrote the manuscript, SLC; SGY; RBD; SGC; SRLO; CPJA: contributed of the final version of this manuscript.

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