RELATO DE CASO
ISSN 1677-5090

Tuberculous Meningitis: a case report of a late diagnosis

Diagnóstico tardio de Meningite Tuberculosa: Relato de Caso

Bruna Tassi Borille[1], Andressa Verzeletti Rodrigues[2], Renata Gonçalves[3], Flávia Martinello[4]

[1]Farmacêutica com habilitação em Análises Clínicas pela Universidade Federal de Santa Catarina. e Mestranda do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade Federal do Rio Grande do Sul, [2]Farmacêutica com habilitação em Análises Clínicas pela Universidade Federal de Santa Catarina, [3]Farmacêutica com habilitação em Análises Clínicas pela Universidade Federal de Santa Catarina e Mestranda pelo Programa de Pós-Graduação em Bioquímica pela Universidade Federal de Santa Catarina mesma Universidade, [4]Farmacêutica com habilitação em Análises Clínicas pela Universidade Federal de Santa Catarina e Mestre pela Universidade Federal de Santa Catarina mesma Universidade. Doutora pelo Programa de Pós Graduação em Farmácia da Universidade de São Paulo, campi Ribeirão Preto, Professora Adjunto do Departamento de Análises Clínicas da Universidade Federal de Santa Catarina.

Abstract

Introduction: *Tuberculous meningitis (TM) is the most severe form of tuberculosis, it has high morbidity and mortality. Once it is diagnosed early, treatment response is excellent.* ***Objective:*** *To report and discuss a case of delayed diagnosis of TM.* ***Methodology:*** *It was selected a case from University Hospital of Federal University of Santa Catarina, the analysis of medical records was performed and discussed based on the scientific literature.* ***Results:*** *It was reported the case of a patient that was diagnosed with leukocytoclastic vasculitis (LV) for six months and was admitted presenting granulomatous lung injury, weight loss, fever and dry cough for eigth months. The delay in the diagnosis of tuberculosis (TB) allowed an evolution to TM and the late onset of treatment impaired the patient's prognosis. It was discussed the vasculitis as a first symptom of tuberculosis, which can occur by deposition of immune complexes formed by antibodies against antigens of bacilli in the vascular wall.* ***Conclusions:*** *Previous diagnosis of LV deviated the focus of the case for their cause, and suggested other pathologic conditions, which contributed to delay in the diagnosis of TB. Despite the late diagnosis and treatment, the therapeutic approaches used for vasculitis, TB and TM followed the protocols described in the literature.*
Keywords: *Tuberculous meningitis cutaneous leukocytoclastic vasculitis.*

Resumo

Introdução: A meningite tuberculosa (MT) é a forma mais grave de tuberculose, apresentando alta morbi-mortalidade. Sendo o diagnóstico precoce, a resposta ao tratamento é excelente. **Objetivo:** Relatar e discutir um caso de diagnóstico tardio de MT. **Metodologia:** Foi selecionado um caso do Hospital Universitário da Universidade Federal de Santa Catarina, realizada análise do prontuário e discutido com base na literatura científica. **Resultados:** Relata-se o caso de uma paciente com diagnóstico há seis meses de vasculite leucocitoclástica (VL), internada apresentando lesão pulmonar granulomatosa, emagrecimento, febre e tosse seca há 8 meses. O atraso no diagnóstico da tuberculose (TB) que permitiu a evolução para MT, e o início tardio do tratamento prejudicaram o prognóstico da paciente. Discute-se a vasculite como primeiro sintoma da TB, que pode ocorrer pelo depósito de imunocomplexos, formados por anticorpos contra antígenos do bacilo, na parede vascular. **Conclusão:** O diagnóstico prévio de VL desviou o foco do caso para a pesquisa da sua causa, sendo sugeridas outras patologias, o que contribuiu para a demora do diagnóstico de TB. Apesar do diagnóstico e tratamento tardios, as alternativas terapêuticas instituídas para a vasculite, TB e MT seguiram os protocolos descritos na literatura.
Palavras-chave: Tuberculose Meníngea. Vasculite Leucocitoclástica Cutânea.

INTRODUCTION

Tuberculosis (TB) usually infects the lungs, but can also affect other organs such as kidney, bone and central nervous system (CNS) (13). In 2011, the extrapulmonary cases of TB in Brazil reached almost 16% of total cases of TB (14) and approximately 6,3% of these (1,3% of the total) were tuberculous meningitis (TM) (4).

A critical stage in the development of TM is the adjacent deposition of mycobacteria at subarachnoid space or ventricles during the dissemination of bacilli. In face of adequate immune response, caseous or non caseous granulomas can be formed, remaining clinically silent or presenting as intracranial lesions. Post-mortem studies suggest that the rupture of these granulomas could be the first phase of TM (8, 18) inducing the immune response and leading to formation of tuberculous inflammatory exudate surrounding the brain. Communicating hydrocephaly can occur by decrease on

Correspondência / Correspondence: Bruna Tassi Borille. Rua Santa Cecília, 1983, Bairro Rio Branco, CEP 90420-041. Local: Porto Alegre, RS, Brasil. Fone: 55 (45) 9921-1110
Email: bruhhtb@gmail.com

reabsorption of cerebrospinal fluid (CSF) in presence of inflammatory exudate. Tuberculous exudate accumulation can also interrupt the CSF flux through ventricles, leading to obstructive hydrocephaly. The immunologic response can trigger vasculitis in the cerebral veins causing ischemia and cerebral damage, even after therapy (7, 8, 18).

TM presents subacute evolution more slow than others meningitis and is the most severe form of TB (5) with approximately 30% mortality rate in treated patients (1). Prodromal period is characterized by fever, lethargy and anorexia, with coughing or not. Subsequently occur headache, vomiting, paralysis of cranial pairs, meningeal signs, paresis, drop in the level of consciousness and coma (9).

The diagnostic of TM represents a challenge due to similarity with others meningoencephalitis, in particular bacterial meningitis (11). The difficult access to the lesions and the paucibacillary characteristic of the samples, when bacilloscopy is usually negative, also contributes for the multifaceted diagnosis (12). Delay in diagnosis and treatment generally leads to severe complications and even death (15). Despite that, the clinical response to treatment of TM is excellent when there is an early diagnosis and before an irreversible neurological damage (5).

CASE REPORT

A sixty-year-old woman, smoker, with leukocytoclastic vasculitis in inferior members confirmed by histopathological exam six months ago, but negative for immune deposits IgA, IgM, IgG and Anticardiolipin IgM and IgG antibodies, sought medical assistance at emergency of University Hospital of Federal University of Santa Catarina. The patient presented granulomatous pulmonary lesion in left superior lobe, loss of weight, feverish for approximately twenty days and dry cough for eight months. She didn't report dyspnea or dermatologic complains, but presented lethargy, mental confusion, altered behaviour, normal neck motion, without motor deficit and hipercromic scars on inferior members. Leukocytoclastic vasculitis, Wegener's syndrome and TB were suggested to investigate as diagnostic hypotheses.

Two days after the patient presented drop on level of consciousness and pulmonary congestion (which altered the gasometric parameters) (Figure 1), being transferred to intensive care unit (ICU), where the laboratorial diagnosis of TB was

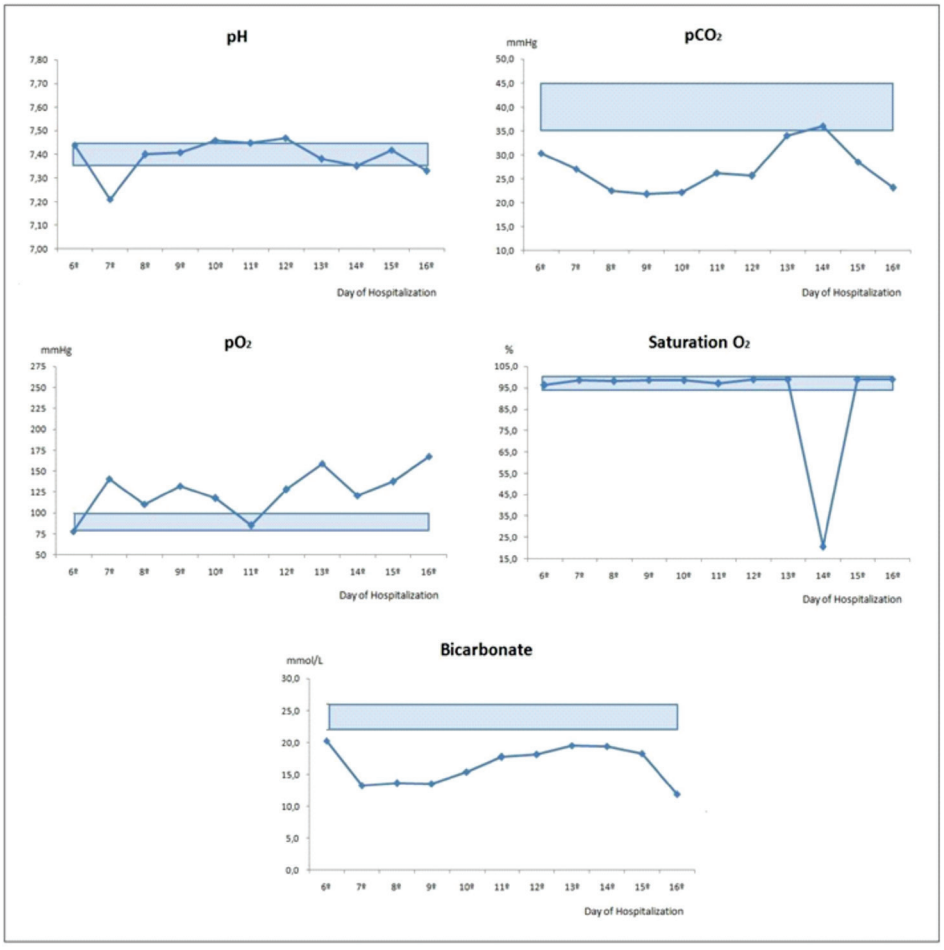

Figure 1. *Evolution of blood gas parameters during the period of hospitalization. The hatched area corresponds to the range of reference values. pH: Potential Hydrogen; PO^2: partial pressure of oxygen; PCO^2: partial pressure of carbon dioxide.*

confirmed and medicamentous treatment was initiated.

The autoantibodies Anti-SM, Anti-La, Anti-RO, c-ANCA, ANA, RF and PPD were not detected. The patient evolved with acute respiratory insufficiency, renal dysfunction (Figure 2) and severe neurological state (stiff neck, bilateral Babinski sign, hydrocephaly and coma).

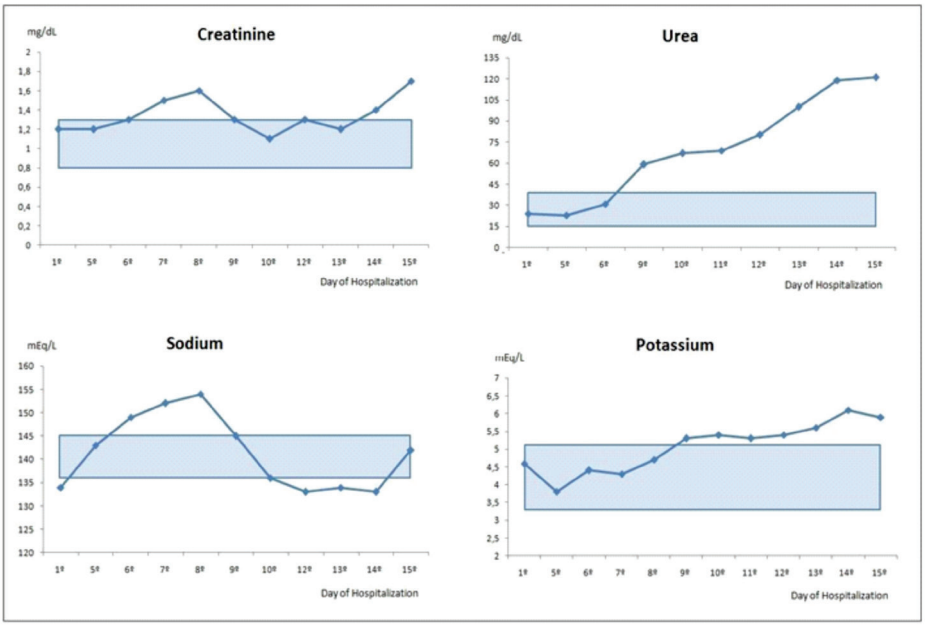

Figure 2. *Evolution of biochemical parameters during the period of hospitalization. The hatched area corresponds to the range of reference values.*

After eleven days at ICU a lumbar puncture was made in order to collect CSF for analysis, which resulted in negative bacterioscopy and culture. Biochemical and cytological analysis presented a slightly yellowish appearance, diminished glucose levels, increased protein levels and cells with predominance of mononuclear.

Corroborating to the diagnosis, computed tomography of brain demonstrated meningeal contrast enhancement, brutal hydrocephaly, diffuse swelling and severe intracranial compliance change, resulting in clinical confirmation of TM. Hyperosmolar therapy was initiated and the patient was conducted to realization of external and internal ventricular derivation on the day after with drainage of 80 mL of CSF, without complications. The patient evolved to irreversible brain damage, which progressed to encephalic death on the 17th day of hospitalization.

DISCUSSION

This case presents a patient with medical history of leukocytoclastic vasculitis and late diagnosis of TM. In the moment of hospitalization, due to previous diagnostic of vasculitis on inferior members, the suspicion of Wegener's Syndrome (WS) was among diagnostic hypotheses. The WS is a vasculitis of small and medium-sized blood vessels associated with antineutrophil cytoplasmic antibodies (ANCAs), being related with positivity of C-ANCA in serum (10). Vasculitis affects mostly respiratory tract and kidneys, and may present nodules and mass (cavitating or not) and lower airway lesions as pulmonary manifestations. Furthermore, there are renal manifestations such as necrotizing glomerulonephritis with crescent formation and poor expression of immunoglobulins (17). Previous leukocytoclastic vasculitis history, pulmonary findings and development of renal dysfunction contributed for suspicion of WS and for delay in the diagnosis and treatment of TM.

However, vasculitis can also be associated with TB, emerging as a first symptom of disease or associated with clinical condition. It has been shown circulating immune complexes on pulmonary TB, with levels related to disease activity. The mechanism of lesion proposed for this type of vasculitis is the deposition of immune complexes (formed by antibodies against antigens of bacillus) on the blood vessel wall rather than direct aggression of bacillus (3). Association of antiphospholipids and anticardiolipin IgA antibodies is reported in leukocytoclastic vasculitis, being that both can be present even in the absence of IgM and IgG forms (2). Although, immune complexes may not be detected in cases of vasculitis associated with TB (3). In this context, the previous negative results of immune complex detection should not have excluded the possibility of the development of vasculitis being associated with immune complexes. In this context, symptoms such as weigh loss, cough and fever are characteristic, and the

visualization of granulomatous nodules in the lung should reinforce the suspicion of TB (12).

Afterwards, pulmonary TB was diagnosed and treatment was initiated (16). Meanwhile, the patient already presented unspecific signs at the admission, such as fever, altered behaviour and mental confusion, which are also common in meningitis (9). Considering these facts, the gradual deterioration of neurological condition was suggestive of meningitis.

The delay in diagnosis and treatment of TM are factors that contribute to a bad prognosis, leading to high mortality and morbidity rates (6, 9). The definitive diagnosis of TM depends mostly on the finding of the bacillus in CSF, by culture or bacilloscopy for detection of acid-alcohol resistant bacilli (AARB). The sensibility of both analyses is low, and culture is a slow process. The CSF analysis is essential for TM investigation, but the diagnostic decision must not depend on finding the etiologic agent, considering the culture analysis can take up to sixty days to be concluded (9). The culture and bacilloscopy sensibility depends on the number and volume of samples, due to paucibacillary nature and irregular distribution of bacillus in CSF (6). Therefore, the decision to treat the patient with specific medication is often empirical, although clinicians are reluctant to start anti-TB treatment without consistent evidence of infection (19). Despite the delay in diagnosis and consequently in treatment, the medicamentous and non-medicamentous therapy realized for the vasculitis, TB and TM followed the protocols described in the literature, but it wasn't able to avoid the negative outcome.

Finally, the analysis of this case allows us to conclude that the previous diagnosis of leukocytoclastic vasculitis diverted the focus of the case to the search of its cause, suggesting other diseases. This fact contributed to the delay in TB and consequently TM diagnosis, complicating the treatment and prognosis of patient.

REFERENCES

1. BARRETO, M.L. Meningitis tuberculosa: claves para su diagnóstico y propuestas terapéuticas. **Rev Chilena Infectol**, Santiago, v.38, n.3, p.238-247, 2011.

2. BRASILEIRO, J.L. et al. Vasculite leucocitoclástica crônica: relato de um caso e revisão bibliográfica. **J Vasc Br**, Birmingham, v.3, n.4, p.392-396, 2004.

3. CARVALHO M. et al. Vasculite leucocitoclástica cutânea associada à tuberculose pulmonar. **J Bras Pneumol**, Brasilia, v.34, n.9, p.745-748, 2008.

4. CHERIAN, A.; THOMAS, S.V. Central nervous system tuberculosis. **Afr Health Sci**, Kampala, v.11, n.1, p.116-127, 2011.

5. AFROZE, D. et al. Improved diagnosis of central nervous system tuberculosis by mpb64- target pcr. **Braz J Microbiol**, São Paulo, v.39, n. 2, p.209-213, 2008.

6. FARINHA, N.J. et al. Tuberculosis of the Central Nervous System in Children: a 20-Year Survey. **J Infect**, London, v. 1, n. 1, p.61-68, 2000.

7. GARCIA-MONCO, J.C. Central Nervous System Tuberculosis. **Neurol Clin**, Philadelphia, v.17, n.4, p.737-759, 1999.

8. HEEMSKERK, D. et al. Intensified treatment with high dose Rifampicin and Levofloxacin compared to standard treatment for adult patients with Tuberculous Meningitis (TBM-IT): protocol for a randomized controlled trial. **Trials**, London, v.12, p.12-25, 2011.

9. HERINGER, R.R. et al. Localização da lesão e achados do líquido cefalorraqueano na meningite tuberculosa: Diferenças nos compartimentos lombar, cisternal e ventricular. **Arq Neuropsiquiatr**, São Paulo, v.63, n.2-B, p.543-547, 2005.

10. KHAN, A. et al. Wegener's granulomatosis: treatment and survival characteristics in a high-prevalence southern hemisphere region. **Intern Med J**, Carlton, v.42, n.4, p.23-26, 2012.

11. KUMAR, R.; SINGH, S.N.; KOHLI, N. A diagnostic rule for tuberculous meningitis. **Arch Dis Child**, London, v.81,n.3, p.221-224, 1999.

12. LOPES, A.J. et al. Tuberculose extra-pulmonar: aspectos clínicos e de imagem. **Pulmão RJ**, Rio de Janeiro, v.15, n.4, p.253-261, 2006.

13. BRASIL. Ministério da Saúde. Secretaria de Vigilância em Saúde. **Guia de Vigilância Epidemiológica**. 7.ed. Brasília, 2009. p.8.

14. BRASIL. Ministério da Saúde. **Brasil reduz casos de tuberculose em 3,54% em 2011**. Disponível em: <http://www.brasil.gov.br/noticias/arquivos/2012/03/26/brasil-reduz-casos-de-tuberculose-em-3-54-em-2011-segundo-ministerio-da-saude>. Acesso em: 28 abr. 2012.

15. BRASIL. Ministério da Saúde. **Doenças infecciosas e parasitárias - Guia de bolso**. 8.ed. Brasília, 2010. p.316-320.

16. BRASIL. Ministério da Saúde. Secretaria de Vigilância em Saúde. **Nota técnica sobre as mudanças no tratamento da tuberculose no Brasil para adultos e adolescentes**. Brasília, 2010.

17. SANTANA, A.N.C. et al. Atualização do tratamento das vasculites associadas a anticorpo anticitoplasma de neutrófilos. **J Bras Pneumol**, Brasília, v.37, n.6, p.809-816, 2011.

18. VINNARD, C.; MACGREGOR, R.R. Tuberculous Meningitis in HIV-Infected Individuals. **Curr HIV/AIDS**,Philadelphia, v.6, n.3, 139-145, 2009.

19. YOUSSEF, F.G. et al. Differentiation of tuberculous meningitis from acute bacterial meningitis using simple clinical and laboratory parameters. **Diagn Microbiol Infect Dis**, New York, v.55, n. 4, p.275-278, 2006.

Submetido em 28.10.2012;
Aceito em 04.04.2013.