Clinical case

Neutrophil-associated Tuberculous Meningitis diagnosed after CSF examination: two case studies

Méningite tuberculeuse à polynucléaires neutrophiles à l’examen du LCR : à propos de deux cas

YK Boussaga¹, F Ihbibane¹, N Sori⁴, N Tassi¹

Abstract
Tuberculous meningitis is a diagnostic and therapeutic emergency. It is classically lymphocytic meningitis. But it can also be in the form of purulent meningitis with a level of neutrophils more or less important in the cerebrospinal fluid. The difficulty of diagnosing atypical forms of this pathology can lead to delayed treatment. We report the clinical cases of two predominantly polynuclear neutrophilic meningoencephalitis in immunocompetent patients. Molecular biology techniques have become unavoidable because they allow rapid diagnosis of Mycobacterium tuberculosis infection and early management of patients, thus improving their life-threatening prognosis, and also decreasing the risk of complications occurring.

Keywords: meningitis, tuberculosis, polynuclear neutrophils.

Introduction
Tuberculous meningitis is a Mycobacterium tuberculosis (MTB) infection of the meninges. It is directly life-threatening. Although rare in developed countries, it remains a common disease in developing countries where TB remains a major public health problem. In Morocco, tuberculosis is endemic. The incidence of tuberculosis was 30,000 cases in 2018 [1] and tuberculous meningitis accounts for about 10% of all localizations [2]. Classically, it is described as a clear fluid meningitis with a high number of neutrophiles. La difficulté du diagnostic des formes atypiques de cette pathologie peut conduire à un retard de prise en charge. Nous rapportons l’observation de deux patientes immunocompétentes traitées pour une méningo-encéphalite tuberculeuse à prédominance polynucléaires neutrophiles. Les techniques de biologies moléculaires sont devenues incontournables car elles permettent un diagnostic rapide de l’infection à Mycobacterium tuberculosis et une prise en charge précoce des patients améliorant ainsi leur pronostic vital.

Mots-clés: méningite, tuberculose, polynucléaires neutrophiles.
predominantly lymphocytic elements, a low glucose level and a high protein level in the cerebrospinal fluid (CSF) [3,4]. Nevertheless, the etiological diagnosis remains a challenge as it can be an often-unknown and poorly described aspect, especially in Africa. We report case studies of two immunocompetent patients treated for tuberculous meningoencephalitis with predominantly polynuclear neutrophil (PNN) cells in the CSF, with the aim of drawing attention to this nosological form which can mislead and delay the diagnosis.

Clinical case

Case 1

Mrs. S M, aged 44, who had been monitored for goitre for 5 years, BCG vaccinated and without any notion of tuberculosis contagion, had been admitted at the infectious diseases department of the Mohammed VI Teaching Hospital in Marrakech for a meningeal syndrome evolving in a context of fever over 15 days. On admission, the patient presented tension-type headache, vomiting, drowsiness, nervousness, photophobia and fever. The clinical examination found a patient with a Glasgow score of 13/15, a frank meningeal stiffness with no focal signs. She was febrile at 38°C, polypneic at 26 cycles per minute, tachycardic at 100 beats per minute, blood pressure was normal at 110/90 mmHg and pulmonary auscultation was normal as was the rest of the clinical examination. Bacterial meningoencephalitis had been suggested as well as severe pneumopathy or severe sepsis with pulmonary onset. The cerebral computed tomography (CT) scan and chest X-ray returned normal. The CSF study found a clear fluid with 1152 elements with predominantly PNN (70%). There was no germ on direct examination or culture on standard media after 24 hours and the multiplex CSF PCR was also negative. Glycorrhachia was reduced to 0.38g/L with a concomitant blood glucose level of 1.20g/L. Proteinorrachia was elevated to 2.75g/L. The rest of the bioassay showed essentially a slight hyperleukocytosis at 11200/mm³, a negative CRP at 4.91 mg/l, and a lowered natremia at 124 mEq/l. In the face of a probable subacute bacterial meningoencephalitis, the patient had benefited from treatment with Ceftriaxone at an initial meningeal dose (70mg/kg/day) but the clinical evolution was stationary after 24 hours. Also, in the context of tuberculosis endemity, a PCR DNA search for MTB in the CSF had been requested with results coming out positive. An antituberculosis treatment was then started according to a 2-month quadritherapy regimen (Rifampicin 10mg/kg/day, Isoniazid 5mg/kg/day, Pyrazinamide 25mg/kg/day and Ethambutol 15mg/kg/day) followed by 7 months of dual therapy (Rifampicin 10mg/kg/day and Isoniazid 5mg/kg/day) combined with corticosteroid therapy: Prednisolone 1mg/kg/d for 3 weeks followed by a gradual decrease over 2 months. CSF culture on Lowenstein solid medium also allowed the isolation and identification of Mycobacterium tuberculosis 21 days after admission. The clinical course was favourable from 48 hours of the start of treatment, as well as throughout the follow-up, without sequelae.

Case 2

Mrs. H L, aged 50, had been admitted at the Mohammed VI Teaching Hospital in Marrakech for mental fog in a febrile context over 14 days. The patient had no significant medical history or notion of tuberculosis contagion. She presented tension-type headache, vomiting and drowsiness. Clinical examination revealed a patient with a Glasgow score of 14/15 with meningeal stiffness and no focal signs. She had a fever of 38.8°C, polyphnea at 30 cycles per minute, tachycardia at 96 beats per minute. Blood pressure was 130/70 mmHg and pulmonary auscultation was normal, as was the rest of the clinical examination. Bacterial meningoencephalitis had been suggested as well as severe pneumopathy or severe sepsis with pulmonary onset. The cerebral CT scan and chest X-ray returned normal. The CSF study found a clear fluid with 1152 elements with predominantly PNN (70%). There was no germ on direct examination or culture on standard media after 24 hours and the multiplex CSF PCR was also negative. Glycorrhachia was reduced to 0.38g/L with a concomitant blood glucose level of 1.20g/L. Proteinorrachia was elevated to 2.75g/L. The rest of the bioassay showed essentially a slight hyperleukocytosis at 11200/mm³, a negative CRP at 4.91 mg/l, and a lowered natremia at 124 mEq/l. In the face of a probable subacute bacterial meningoencephalitis, the patient had benefited from treatment with Ceftriaxone at an initial meningeal dose (70mg/kg/day) but the clinical evolution was stationary after 24 hours. Also, in the context of tuberculosis endemity, a PCR DNA search for MTB in the CSF had been requested with results coming out positive. An antituberculosis treatment was then started according to a 2-month quadritherapy regimen (Rifampicin 10mg/kg/day, Isoniazid 5mg/kg/day, Pyrazinamide 25mg/kg/day and Ethambutol 15mg/kg/day) followed by 7 months of dual therapy (Rifampicin 10mg/kg/day and Isoniazid 5mg/kg/day) combined with corticosteroid therapy: Prednisolone 1mg/kg/d for 3 weeks followed by a gradual decrease over 2 months. CSF culture on Lowenstein solid medium also allowed the isolation and identification of Mycobacterium tuberculosis 21 days after admission. The clinical course was favourable from 48 hours of the start of treatment, as well as throughout the follow-up, without sequelae.
320 elements/mm³ with predominantly PNN (70%), a glycorrhachia lowered to 0.19g/l with a correlating blood glucose level of 1.38g/l, a proteinorrachia raised to 3.23g/l. Direct examination was negative and the culture on standard medium was sterile after 48 hours. The rest of the workup consisted mainly of lymphopenia at 660/mm³ on FBC, low CRP at 33.82 mg/l, and low natremia at 132 mEq/l. Given this picture of subacute meningoencephalitis with miliary opacities in radiology, a PCR on the CSF was requested in search of MTB DNA and the results came back positive. The patient had been treated for TB with corticotherapy in the same manner as the previous patient. The CSF culture on Leowestein solid media was also positive for MTB 14 days after admission. The progression was rapidly favorable at the start of treatment, but an intracranial hypertension syndrome had appeared after one month of correctly followed treatment. Brain CT scan revealed contiguous ring-shaped micro lesions in the sellar region suggestive of tuberculomas (Figure 2). Tuberculosis treatment was maintained and full-dose corticotherapy was continued for 2 months prior to degression. The treatment had been correctly taken without side effects and the outcome was favorable, with no clinical or radiological sequels.

Table: Clinical, Biological and Radiological Characteristics of Patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Development period before admission</td>
<td>14 days</td>
<td>15 days</td>
</tr>
<tr>
<td>Biology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF Aspect</td>
<td>Transparent</td>
<td>Cloudy</td>
</tr>
<tr>
<td>Glycorrhachia</td>
<td>0.38g/l</td>
<td>0.19g/l</td>
</tr>
<tr>
<td>Proteinorrachia</td>
<td>2.75g/l</td>
<td>3.23g/l</td>
</tr>
<tr>
<td>Total number of elements CSF</td>
<td>1152/mm³</td>
<td>320/mm³</td>
</tr>
<tr>
<td>Percentage of polynuclear cells CSF</td>
<td>70%</td>
<td>70%</td>
</tr>
<tr>
<td>Direct Examination CSF</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>CSF Culture in unspecified medium</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Test Xpert CSF</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Culture/Loewenstein CF</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Natremia</td>
<td>124 mEq/l</td>
<td>132 mEq/l</td>
</tr>
<tr>
<td>FBC: White Blood Cells</td>
<td>11200/mm³</td>
<td>8000/mm³</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1110/mm³</td>
<td>660/mm³</td>
</tr>
<tr>
<td>CRP</td>
<td>4.91 mg/l</td>
<td>33.82 mg/l</td>
</tr>
<tr>
<td>HIV Serology</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Radiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial Cerebral CT Scan</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Chest X-Ray</td>
<td>Normal</td>
<td>Miliary</td>
</tr>
</tbody>
</table>

Figure 1: Chest X-ray showing miliary image (Patient 2)

Figure 2: Cerebral CT scan showing a tuberculoma (Patient 2)
Discussion

In both patients, meningoencephalitis with pus cells was observed. Having the appropriate technical platform, we were able to carry out PCR in search of MTB DNA, which allowed us to make the diagnosis very quickly thereafter. The multiplex PCR also allowed us to clear up the ambiguity of a possible infection with common germs. Tuberculosis treatment could be started as soon as the diagnosis was confirmed.

Nevertheless, whereas for the second case diagnosis was easy and quick to make in the face of miliary opacities discovered on chest X-ray, for the first patient the hypothesis of meningoencephalitis was only raised in the face of the unfavorable evolution after 24 hours of correctly conducted antibiotic treatment, which delayed diagnosis. In this case, the initiation of antibiotic therapy targeting both common germs and MTB could have been justified. However, in Morocco, national recommendations on the use of antituberculosis treatments require microbiological evidence in order to slow down the emergence of resistance to these molecules. In addition, no new analysis of the CSF was performed to determine the kinetics of PNN. Indeed, neither case warranted another lumbar puncture.

We mentioned tuberculous meningoencephalitis in the context of tuberculosis endemicity in Morocco, the progressive appearance of symptoms and their subacute evolution, the moderate inflammatory syndrome in the blood work, the absence of germ on direct examination after Gram staining and CSF culture and the presence of a radiological miliary opacities for the second patient.

The appearance of cerebral tuberculomas in one of the patients after one month, despite a well-conducted treatment, shows a paradoxical evolution of this pathology. It involves the appearance of new symptoms or a transient, clinical and/or radiological increase in pre-existing tuberculous lesions, even though the treatment was adapted and correctly taken. This phenomenon corresponds to an immune reconstitution syndrome [5-7].

The predominance of PNN in the CSF during tuberculous meningitis is rare and the kinetics of their occurrence varies from patient to patient. A few authors report the discovery of PNN-dominant pleocytosis at the time of diagnosis. This is the case of VL Pinto et al in 2008 in Brazil who described 3 cases occurring between 2000 and 2005; and SM Dimitriu et al who described 14 cases occurring over 20 years (from 1958 to 1972) in Romania [3,8]. Indeed, these PNN can appear at the beginning of the infection with a progressive evolution towards a reversal of the formula in favor of polymuclear lymphocyte cells with disappearance of the PNN [3]. This form simulates the appearance of purulent meningitis decapitated by antibiotic therapy that is often badly conducted. Sometimes, the appearance of PNN is seen during the course of evolution, as described by Hutin et al 2016, with a lymphocyte pattern at the beginning of the infection, which gradually becomes PNN predominant followed by a new inversion of the pattern in the CSF in favor of lymphocytes [9]. A third form is distinguished by the predominance of PNN in the CSF which is observed at the time of diagnosis of tuberculous meningitis and their persistence throughout the follow-up of the patient until the total disappearance of nucleated cells in the CSF without inversion of the formula thus simulating purulent meningitis [8]. The conditions of appearance and evolution of these cells remain unknown for the moment.

The effective management of tuberculous meningitis relies primarily on the capacity of biological diagnosis. Microscopy, a simple and easy to perform technique, although not very sensitive, is still recommended because it allows rapid diagnosis of tuberculosis. However, its sensitivity is correlated with a high bacterial load [10]. MTB culture remains the reference technique for the diagnosis of tuberculosis. Its specificity is absolute and its sensitivity better than that of microscopy and molecular methods [11-12]. It allows confirmation of cases, negative microscopic diagnosis of tuberculosis, detection of false negatives.
by molecular methods, and determination of antibiotic sensitivity of isolated strains. However, this technique is of little contribution to the urgency of neuromeningeal tuberculosis because it requires between 10 and 60 for its realization [12,13]. Molecular methods are recommended as a first-line treatment because they allow rapid (within 2 hours) and reliable detection of the DNA of the MTB complex with a sensitivity and specificity that varies between 70 and 95%, depending on the authors, with a high negative predictive value [10,14]. However, the performance of these techniques would not completely cover the diagnosis of tuberculosis with negative microscopy and extra pulmonary forms [12,15]. Thus, there is still a risk of false negatives. Moreover, these methods do not distinguish between living and dead microorganisms [11,12]. In any case, the presence of MBT DNA in the CSF requires immediate initiation of tuberculosis treatment because of the life-threatening nature of the disease and the risk of brain sequelae. In addition to these techniques aimed at directly identifying the bacillus or its genome, complementary techniques are currently available to support the suspicion of TB. For example, adenosine deaminase (ADA) activity can be measured in the CSF after eliminating purulent or opportunistic meningitis (cryptococcosis, toxoplasmosis), which are also causes of increased ADA [11]. Similarly, gamma interferon (IFNγ), which is produced by the patient’s T cells in the presence of MTB-specific antigens, can be tested in the blood. A negative serum assay for IFNγ corresponds to the absence of patient contact with the bacterium [15]. Finally, the etiologic investigation should systematically include chest imaging for lung lesions, eye fundus examination and HIV serology [11].

**Conclusion**

Tuberculous meningitis or meningoencephalitis can have a purulent appearance. It must be discussed in the face of any subacute meningitis, particularly in endemic areas. It is a rare form and little described in literature, thus likely to mislead clinicians. It should be investigated because, like lymphocytic tuberculous meningitis, it is associated with significant morbidity and lethality in the event of error or delay in diagnosis. The etiological investigation involves careful questioning, physical examination, and targeted and directed paraclinical assessment to confirm the diagnosis and refute other hypotheses. The management and the evolution are identical to that of lymphocytic tuberculous meningitis.

**Contributions of authors**

Fatima Ihbibane: Reading and correction of manuscript. Nabila Soraa: Reading and correction of manuscript. Noura Tassi: Reading and correction of manuscript.

**Appreciation**

Tsoumbou Bakana Gladys: for manuscript review. Samuel Opoku Gyamfi: for translation

*Correspondence*

Yvonne Komba Boussaga

kbyvonne@gmail.com

**Available online**: December 2, 2020

1: Service des Maladies Infectieuses – CHU Mohammed VI – Université Caddy Ayad – Marrakech
2: Service de microbiologie – CHU Mohammed VI – Université Caddy Ayad – Marrakech

© Journal of african clinical cases and reviews 2020

**Conflicts of interest**: None
References


To cite this article: