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Case Report

Primary Whipple disease of the Central Nervous System presenting with rhombencephalitis

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ABSTRACT

Primary Whipple disease of the Central Nervous System is a rare entity whose outcome might be fatal if not promptly diagnosed and treated. Few cases are reported in the literature with heterogeneous clinical and radiological presentations which often make the diagnosis extremely challenging.

We report a case of primary Whipple disease of the Central Nervous System presenting with rhombencephalitis in a female patient in immunosuppressive treatment for rheumatoid arthritis. We describe the management of our patient and discuss the features of this rare clinical entity.

Introduction

Central Nervous System (CNS) involvement during Whipple's disease (CNS-WD) can complicate the classic form, or less frequently, present as a primary localization, in particular in immunocompromised patients (Marth et al., 2016). Primary CNS-WD is a clinical challenge, representing a life-threatening but treatable condition. Herein, we report on an immunocompromised patient who developed primary CNS-WD presenting as rhombencephalitis, with the aim of facilitating prompt diagnosis of this rare disease.

Case report

The patient was a 76-year-old woman admitted to our Neurology ward because of subacute onset of diplopia, vertigo, postural instability and headache. She had a 9-year history of rheumatoid arthritis in treatment with methotrexate and low-dose steroids (prednisone 2.5 mg) and reported penicillin allergy.

On admission, neurological examination revealed bilateral ptosis, diplopia in all gaze positions and right dysmetria. Blood tests showed 11520 leukocytes/mm^3 with normal C-Reactive Protein (CRP). Brain angio-CT scan was normal.

Soon after admission the patient experienced rapid consciousness deterioration with cranial nerve deficits and ataxic paresis of the right upper limb. Lumbar puncture showed crystal clear cerebrospinal fluid (CSF) with moderate mononuclear pleocytosis (52 cells/mm^3), mildly elevated proteins (106 mg/dl) and normal glucose. Molecular amplification for viruses (EBV-DNA, HSV1/2-DNA, CMV-DNA, VZV-DNA, HHV6-DNA, Enterovirus-RNA, Polyomavirus-JC-DNA PCR), *M. tuberculosis* and *Toxoplasma* on CSF as well as CSF culture resulted negative. Despite negative microbiological results on CSF, due to increasing leukocytes (15610/mm^3) and CRP (8 mg/dL), meropenem (2 g q8h) was started. On the same day in which antibiotics were started, signs of brainstem involvement with tachycardia, tachypnoea, miosis and ataxic quadriplegia appeared, requiring mechanical ventilation in the Intensive Care Unit (ICU). During the ICU stay, brain MRI was performed, showing multiple contrast-enhancing lesions involving the pons, medulla and cerebellum, suggestive for rhombencephalitis. Similar lesions involved the cervical spinal cord and the right trigeminal nerve (see Figure 1).

Considering the radiological findings, linezolid and cotrimoxazole were introduced to empirically cover Nocardia and Toxoplasma.

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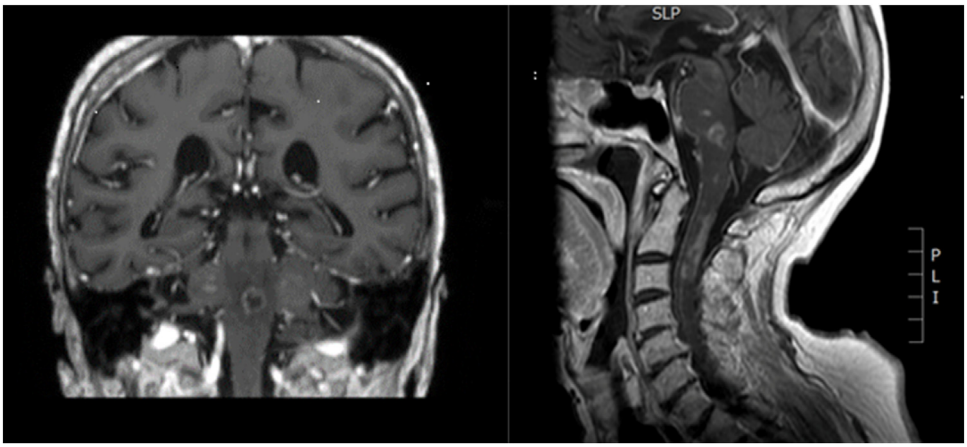

Figure 1. MRI showing contrast enhancing lesions in involving pons, medulla and cerebellum, suggestive for rhombencephalitis. Similar lesions are evident on the proximal tract of the cervical spinal cord.

However, toxoplasma serology resulted negative, as well as HIV test. Total-body CT scan also resulted normal.

During wide-spectrum antibiotic therapy, the patient experienced progressive improvement of the consciousness level allowing ICU discharge after few days. Clinical improvement was confirmed by a brain MRI performed after 2 weeks of antimicrobial treatment revealing a reduction of the brainstem lesions.

CSF analysis performed after 1 month of antibiotic treatment confirmed the general improvement (18 cells/mm^3; proteins 57 mg/dL): this time, CSF was sent for further analysis including *Tropheryma whipplei*-PCR, which resulted positive (genotype 2A).

After this finding, antimicrobial therapy was de-escalated by continuing oral cotrimoxazole only (160/800 mg q12 h) and the patient was discharged overall in good clinical condition, although still affected by diplopia in horizontal gaze, right seventh nerve cranial deficit and ataxic hemiparesis. After a 6-month rehabilitation course, esophagogastroduodenoscopy was performed, showing negative Periodic Acid Schiff (PAS) staining and *T. whipplei*-PCR on multiple duodenal biopsies. Furthermore, a 6-month follow-up brain MRI showed complete resolution of cerebral lesions, while a 12-month follow-up lumbar puncture revealed normal CSF with negative *T. whipplei*-PCR.

During antibiotic treatment the patient experienced complete resolution of ocular and cranial nerve disorders, while mild hemiparesis persisted as long-term sequela. Cotrimoxazole was continued for 18 months and due to rheumatoid arthritis reactivation, steroids and methotrexate were subsequently reintroduced. The patient is currently 16 months post-antibiotics suspension in overall discrete clinical conditions; nonetheless, follow-up is still ongoing in order to monitor for possible relapses.

Discussion

Very few cases of primary CNS-WD confirmed by histological or microbiological examination with consensual negative gastrointestinal specimens are reported in the literature (Mohamed et al., 2011; Sung et al., 2012; Balasa et al., 2014; Panegyres et al., 2006; Peregrin and Malikova, 2015; Giaccone et al., 2016; Tábuas-Pereira et al., 2016; Kilani et al., 2018).

Neurological presentation of CNS-WD is heterogeneous (Marth et al., 2016; Mohamed et al., 2011; Panegyres et al., 2006): cognitive changes and psychiatric symptoms are common, followed by hypothalamic symptoms, myoclonus and ataxia (Louis et al., 1996). Ocular movement disturbance, including oculomasticatory myorhythmia or oculo-facio-skeletal myorhythmia associated with progressive supranuclear ophthalmoplegia, are considered pathognomonic of CNS-WD although rarely reported (Louis et al., 1996) Overall, the triad of dementia, ophthalmoplegia and myoclonus is considered highly suggestive (Louis et al., 1996).

Similarly, there is no typical neuro-radiologic pattern of CNS-WD that can present with multifocal lesions often involving the hypothalamus, thalamus, midbrain or temporal lobes (Panegyres et al., 2006; Tábuas-Pereira et al., 2016), as well as with a focal lesion with or without mass effect (Peregrin and Malikova, 2015; Giaccone et al., 2016; Kilani et al., 2018) or even with normal radiological pattern (Sung et al., 2012).

Our patient presented with some of the typical symptoms of CNS-WD including ocular movementsdeficits and ataxia, while brainstem involvement is quite uncommon. Listeria is the most common cause of infectious rhombencephalitis, followed by Enterovirus-71 (Jubelt et al., 2011), while to our knowledge, no cases of CNS-WD presenting with rhombencephalitis have been previously reported.

Despite being very uncommon, spinal cord involvement has also been described in CNS-WD (Balasa et al., 2014; Gerard et al., 2002) and our patient seems to reflect this uncommon localization; of note, Gerard et al suggest that WD, although rare, must be considered in case of inflammatory spinal involvement (Gerard et al., 2002).

Immunosuppression plays a major role in predisposing to WD (Marth et al., 2016). Notably, misdiagnosis of WD-associated arthralgias as rheumatic disorders can lead to inappropriate immunosuppressive therapies accelerating the natural history of the infection (Glaser et al., 2017). In our patient, the positivity of the anti-citrullinated peptide/protein antibodies (anti-CCP) and the previous benefit of steroids on arthralgias made the diagnosis of rheumatoid arthritis likely even before excluding a systemic disease by endoscopy.

The delay in performing the duodenal biopsies is certainly a limitation of our case report since the intestinal abnormalities might have improved during antibiotic course. However, studies demonstrate how even after successful eradication of *T. whipplei*, the PAS-positive material in macrophages of duodenal lamina propria can persist for several years; moreover, the endoscopic lesions are likely to last longer than 6 months in more than 80% of cases (Geboes et al., 1992). As recommended, multiple biopsies were taken in our patient in order to increase the sensitivity in case of patchy histopathological alterations (Marth et al., 2016).

Untreated WD has a fatal course. A 2-week induction phase with ceftriaxone or meropenem followed by cotrimoxazole is proposed as standard treatment for CNS-WD (Marth et al., 2016).

However, clinical failures with cotrimoxazole have been reported, partly associated to mutations in the *folP* gene encoding dihydropteroate-synthase, the sulphonamides target (Lagier et al., 2014). The association of doxycycline with hydroxychloroquine represents a valid alternative option. Given her allergy to penicillin, our patient was initially treated with meropenem and afterwards with cotrimoxazole to empirically cover toxoplasma. Hence, she luckily received an appropriate scheme for CNS-WD even before the diagnosis was made, allowing clinical improvement.

The duration of treatment for classic WD is usually one year, and follow-up duodenal biopsies are warranted to monitor treatment response (Marth et al., 2016). Differently, treatment duration for CNS-WD remains controversial (Mohamed et al., 2011) as late relapses have been described after antibiotics discontinuation, associated with a severe prognosis (Marth et al., 2016); therefore some experts recommend life-long suppression with doxycycline. In general, a negative PCR on follow-up CSF is considered a good marker of therapeutic efficacy (Marth et al., 2016).

The clinical improvement observed in our patient, together with the complete resolution of radiological signs at 6-month follow up MRI and the negativity of *T.whipplei* PCR on 1-year follow up CSF, led us to discontinue cotrimoxazole after 18 months. However, given the reintroduction of immunosuppressive treatment for rheumatoid arthritis, the patient is being closely monitored for potential relapse.

Conclusions

Isolated CNS-WD is a clinical challenge and should be considered in the differential diagnosis in unusual cases of encephalitis. Awareness among clinicians should be raised in order to help prompt diagnosis and optimal treatment.

As the exact treatment duration of CNS-WD has not been established, patients should be closely followed in case of antibiotics discontinuation in order to monitor for potential relapse, especially in case of coexisting immunosuppression.

Consent for publication

Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

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Conflict of interest

The authors declare that there is no conflict of interest regarding this publication.

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