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Neuronavigation-guided biopsy for differential diagnosis of pseudotumoral demyelinating brain lesions

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ABSTRACT

Marburg's disease (MD) is an extremely rare and aggressive form of multiple sclerosis (MS). In some cases, MD presents with tumefactive demyelinating lesions with a "tumor-like" appearance in MRI images, for which it may be difficult to achieve a form of differential diagnosis between definitive tumors or abscesses. Here we report a case of MD histopathologically confirmed after neuronavigationguided biopsy. Postoperative course was uneventful and following discharge, the patient attended outpatient follow-up appointments and received i.v. cyclophopsphamide, achieving progressive clinical remission. A nine-month follow-up brain MRI scan with gadolinium showed no signs of progressing demyelinating disease with an evident reduction of the biopsied lesion, and almost complete retrogression of the other two lesions.
In our opinion, and through the analysis of currently available literature, early neuronavigation-guided biopsy is a highly recommend, valuable, and safe diagnostic tool; it is also preferable to stereotactic biopsy, since its benefits include a very low bleeding rate and brain damage risk, with minimum mortality and morbidity rates. It also allows the identification of the specific histological pattern, helping to select the best medical treatment approach and contributing to increase patient outcome and life expectancy.

Introduction

"Pseudotumoral demyelinating lesions" comprise various forms acute demyelinating processes characterized by significant difficulties in reaching a differential diagnosis excluding gliomas, tumors and abscesses [1]. Two nosological entities, Marburg's disease (MD) and acute disseminated encephalomyelitis (ADEM), are associated with similar findings. While MD affects exclusively white matter fibers, grey matter involvement is not unusual in ADEM; moreover, the onset of the latter often occurs following infection or vaccination. MD is an extremely rare and aggressive form of Multiple Sclerosis (MS) with acute onset, rapid and severe neurological deterioration, and poor prognosis, usually less than one year. From a histopathological point of view, MD is similar to classical MS, but lesions are often bigger with more inflammatory infiltrates. In some cases, MD presents with a single, voluminous lesion with perilesional edema. In magnetic resonance (MRI) images, MD lesions display mild focal enhancement or typical ring enhancement. Furthermore, the rapid neurological deterioration coincides with a fast growth rate on MRI. The definite diagnosis is often delayed, possibly due to the atypical clinical and radiological aspects described above. In recent years, there has been increasing interest in use of surgical biopsies to reach a certain and early diagnosis, in order to determine the appropriate therapeutic approach avoiding unnecessary surgical or radiation treatment [2,3]. Here we report a histopathologically confirmed case of MD. Furthermore, we discuss measures to improve the diagnostic procedure and timing of best treatment to improve the prognosis, through the analysis of currently available literature.

Case report

A 24-year-old woman presented with a sudden onset of speaking difficulties and hemifacial numbness on the right side. Her past medical history was unremarkable, and she was not taking any medications at the time. A neurological exam at admission revealed mild right facial deficit and borderline motor aphasia. After a few hours, a rapid neurological deterioration with mild pyramidal right hemiparesis and complete aphasia were observed. The patient underwent a brain CT scan that showed three vague hypodense lesions: a large one in the left frontal white matter, and two smaller lesions in the parietal and the right paratrigonal white matter. On MRI

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with gadolinium, the lesions in the paratrigonal and parietal white matter appeared as highly hyperintense on TSE-T2 and FLAIR-T2 sequences, hypointense on TSE-T1, and responsible for a moderate mass effect on the surrounding structures with incomplete ring enhancement and choroid plexus involvement, possibly due to congestion. The frontal lesion showed a pseudotumoral aspect, was mildly hyperintense on TSE-T2 and FLAIR-T2, strongly hyperintense on DWI with atypical patchy enhancement (Fig. 1A–B). Our first hypothesis was ADEM or a severe form of MS. Differential diagnostic options included tumors and abscesses. Thus the patient underwent total body CT scan that did not reveal additional lesions. Blood chemistry screens did not reveal any abnormalities. Autoantibodies and virology testing in the blood and in the cerebrospinal fluid (CSF) were negative, but agarose gel isoelectric focusing detected the presence of oligoclonal bands in the CSF. So, we hypothesized an acute form of demyelinating disease. The patient was therefore treated with steroids without significant improvement. Taking into account all data, we performed a neuronavigation-assisted biopsy of the main lesion using an open microsurgical approach. On the day before the surgery, markers were positioned on the patient's scalp for neuronavigation guidance. Preoperative planning was then carried out using a contrast agent-enhanced computed tomography (CT) scan of the brain. The obtained CT images were transferred to a data storage device, and subsequently were inserted into the neuronavigator. After anaesthesia induction, the principal landmarks established during the planning phase were identified. A neuronavigation-assisted parietotemporal craniotomy was performed, followed by a small corticectomy centered on the lesion. The affected gelatinous and whitish portion of tissue was identified at a depth of about 2 cm, removed in small fragments and sent for histological analysis. A postoperative CT scan ruled out any complications and the postoperative course was uneventful (Fig. 1C).

Neurological exam at discharge was slightly better, with partial reversion of the hemiparesis and improved speech function. The histopathological report confirmed our hypothesis of MD.

Immunohistochemistry was performed on thin sections to evaluate the presence of glial fibrillary acidic protein (GFAP), related to reactive astrocytosis, and of myelin basic protein (MBP), typically absent in demyelinating areas. Marked gliosis and large areas of demyelination in the white matter, characterized by the absence of MBP, were observed.

Immunohistochemistry was also performed to determine positivity for the CD3 and CD68 antigens, expressed in perivascular T-lymphocytes and macrophages, respectively. Isolate perivascular lymphocyte infiltration with a marked gliosis was observed as a result of a massive reactive astrocytosis. Based on the pathological classification system proposed by the Multiple Sclerosis Lesion Project (MSLP) [4], the lesion could be graded as pattern I (T-cell/macrophage-associated).

Following discharge, the patient attended outpatient follow-up appointments and received i.v. cyclophosphamide, achieving progressive clinical remission. A nine-month follow-up brain MRI scan with gadolinium showed no signs of progressing demyelinating disease with an evident reduction of the biopsied lesion, displaying low peripheral enhancement, nearly absent mass effect, and almost complete retrogression of the other two lesions (Fig. 1D-E).

Discussion

Four immunopathological patterns of demyelinating disease have been proposed by Lucchinetti in the Multiple Sclerosis Lesion Project (MSLP) [4]. These patterns are related to the grade of myelin protein loss, the geography and extension of plaques, the extent of oligodendrocyte destruction, and the immunopathological evidence of complement activation. The classification described by Lucchinetti is useful for diagnostic and therapeutic purpose. Pattern I is T-cell/macrophage associated; pattern II is antibody/complement associated and shows similarities with T-cell plus antibody-mediated autoimmune encephalomyelitis; pattern III is expression of distal oligodendrogliopathy; in pattern IV there is oligodendrocyte dystrophy in the periplaque white matter. These last two patterns are

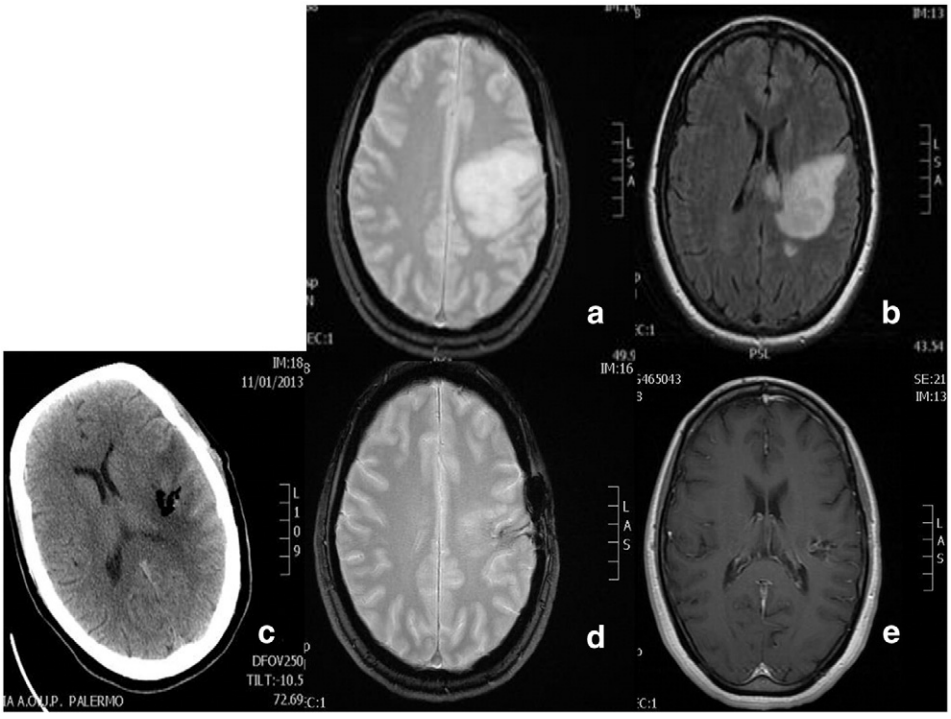

Fig. 1. a–b: Pseudotumoral aspect of the left fronto-parietal lesion. c: Immediate postoperative CT scan. d–e: Nine-month follow-up brain MRI scan showing no signs of progressing demyelinating disease and almost complete retrogression of the other two lesions.

similar to a virus or toxin-induced demyelination rather than an autoimmune process.

Maybe, as suggested by Barnett (2004) [5], all demyelinating lesions originate from a widespread apoptosis of the oligodendrocytes without contemporary active inflammatory demyelinaton signs, and only subsequently they evolve into one of the four patterns.

There is no clear relationship between the specific immunopathological feature and the clinical course with its related prognosis. However, the use of surgical biopsy for anatomopathological characterization of the demyelinating lesions, is necessary for the best therapeutic management and, finally, to ameliorate the outcome.

For this reason even if classically considered an exclusively neurological pathology, MS has recently become a disorder of growing importance for neurosurgeons. In fact, in the rare cases characterized by a sudden onset of neurological symptoms associated with tumefactive demyelinating lesions with a "tumor-like" appearance in MRI images, reaching a definitive differential diagnosis is difficult; moreover, oligoclonal bands may be absent in the CSF, albeit extremely rarely [1]. In previous reports several demyelinating lesions have been described as "tumor-like" from a clinical point of view, and especially in relation to their distinctive radiological features [1,2]. Young adults are more frequently affected. Although diagnostic approaches without biopsy have been attempted by employing more and more sophisticated radiological studies and CSF analyses, histological evaluation is still essential to achieve a definite diagnosis in some of the more complicated cases. Stereotactic or neuronavigation-guided biopsies are considered two of the least invasive approaches, offering low bleeding, mortality and morbidity rates. Moreover, obtaining and analysing a tissue specimen is sure to lead to an almost certain diagnosis. A previous study by Maarouf and colleagues [2], carried out in a population of six patients with pseudotumoral demyelinating lesions that were treated surgically (five stereotactic biopsies and one microsurgical resection), reported no postoperative complications, and improved clinical courses in all cases after a few months of adequate therapy. In one case, the results of a neurological examination after three months were almost normal. The mean mortality rate associated with stereotactic biopsies is estimated in current literature to be about 0.8%, following the introduction of CT and MR imaging-based surgical planning. Maarouf and colleagues reported a bleeding rate of 0.5% [2]. Based on the analysis of the literature, the majority of pathologically confirmed cases of tumefactive demyelinating lesions are diagnosed through open craniotomies [6] and stereotactic biopsies [2], and, only rarely, through neuronavigation-assisted biopsies [3]. This is surprising since neuronavigation may simplify the surgical procedure, carries low surgical risks and provides a reliable histological diagnosis.

Considering the total duration of the surgical procedure, the related risks, and the possibility of obtaining suitable samples, neuronavigation should be the preferred biopsy technique, according to both our experience and the available literature. The advantages consist in: 1) neuronavigation assisted biopsy can be performed also in a department without access to stereotactic equipment, 2) may be less costly and less time consuming than stereotactic procedures; indeed, although the neuronavigation-guided procedure may seem to entail a longer surgical time, the lengthy planning phase of the stereotactic approach greatly extends the overall duration of the latter procedure. Moreover, due to the enhanced field of view, neuronavigation allows for superior bleeding control and the collection of larger samples that are better suited for histopathological evaluation. Because of these advantages, neurologists (and neurosurgeons) may consider biopsy as a diagnostic tool more frequently than it is current clinical practice.

Disadvantages of this technique consist in: 1) limited accuracy, as compared with stereotaxy, especially for small lesions, 2) the lack of clinical trials comparing neuronavigation techniques and classical stereotaxy.

On the basis of the available data, the standard initial therapeutic management of MS should be pharmacological. However, in some atypical cases, CSF analysis, MRI imaging and/or clinical evaluation are not sufficient to rule out tumors or abscesses. Positivity for oligloclonal bands is not an exclusive characteristic of demyelinating processes, since it can also be related to malignant tumors; furthermore, not all demyelinating lesions are associated with oligoclonal band positivity. Radiologic evaluation is often insufficient, especially in cases with large and/or isolated lesions with atypical enhancement after contrast medium administration.

Our case illustrates that in such cases early neuronavigation-guided biopsy may serve as a valuable and safe diagnostic tool.

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