A BIOPSY-VERIFIED CASE OF CENTRAL NERVOUS SYSTEM INVOLVEMENT OF MYCOSIS FUNGOIDES WITH POSITIVE RT-QUIC ASSAY

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ABSTRACT

Introduction: We report a rare case of positive RT-QuIC assay in CNS involvement of mycosis fungoides. **Case presentation:** A 73-year-old man presented with decreased consciousness and generalised convulsions. He had been formerly diagnosed with mycosis fungoides, by that time in full remission. Clinical examination revealed profound cognitive deficits with fluctuating level of alertness during admission. An MRI of the brain showed multiple contrast-enhancing lesions in both hemispheres, while lumbar puncture indicated lymphocytic pleocytosis with elevated CSF protein. The rapidly progressive cognitive decline prompted investigations for Creutzfeldt-Jakob disease (CJD) with 14-3-3 and RT-QuIC assay, both of which came back positive. Meanwhile, flow cytometry analysis reported increased T-cell population, suggestive of CNS lymphoma. Despite the high specificity of the RT- QuIC assay for CJD, the diagnosis was not further supported by imaging or EEG findings. A brain biopsy was performed, reporting brain infiltration by a highly malignant T-cell lymphoma, believed to represent large cell transformation of mycosis fungoides with CD30 expression. Treatment with pulsed steroids had some effect on the level of consciousness, although a degree of memory impairment remained. **Conclusion:** Positive RT-QuIC assay has been strongly linked to CJD, with specificity reaching 99%. This case highlights the possibility of positive RT-QuIC results associated with CNS lymphoma.

Keywords: mycosis fungoides, Creutzfeldt-Jakob syndrome, status epilepticus, T-cell lymphoma

ΜΙΑ ΠΕΡΙΠΤΩΣΗ ΙΣΤΟΛΟΓΙΚΑ ΕΠΙΒΕΒΑΙΩΜΕΝΗΣ ΠΡΟΣΒΟΛΗΣ ΤΟΥ ΚΕΝΤΡΙΚΟΥ ΝΕΥΡΙΚΟΥ ΣΥΣΤΗΜΑΤΟΣ ΑΠΟ ΣΠΟΓΓΟΕΙΔΗ ΜΥΚΗΤΙΑΣΗ ΜΕ ΘΕΤΙΚΗ ΔΟΚΙΜΑΣΙΑ RT-QUIC

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ΠΕΡΙΛΗΨΗ

Εισαγωγή: Παρουσιάζουμε σπάνια περίπτωση θετικής ανάλυσης RT-QuIC σε ασθενή με προσβολή του κεντρικού νευρικού συστήματος από σπογγοειδή μυκητίαση. **Παρουσίαση του περιστατικού:** Άνδρας 73 ετών μεταφέρθηκε σε ληθαργική κατάσταση στο Τμήμα Επειγόντων μετά από γενικευμένους τονικοκλονικούς σπασμούς. Κατά το παρελθόν είχε διαγνωστεί με σπογγοειδή μυκητίαση, σε πλήρη ύφεση πλέον. Κατά την νοσηλεία παρουσίαζε κυμαινόμενο επίπεδο συνείδησης και νοητική έκπτωση. Η μαγνητική τομογραφία εγκεφάλου έδειξε πολλαπλές βλάβες με σκιαγραφική ενίσχυση και στα δύο ημισφαίρια, ενώ στην οσφυονωτιαία παρακέντηση διαπιστώθηκε λεμφοκυτταρική πλειοκύτωση με αυξημένο λεύκωμα. Λόγω της ταχέως εξελισσόμενης ανοϊκής συνδρομής χαρακτηριζόμενης από διαταραχές μνήμης, προσανατολισμού σε τόπο και χρόνο, συγχυτικοδιεργετικά επεισόδια και ΗΕΓφική εικόνα βαρείας εγκεφαλοπάθειας, προγραμματίστηκε διερεύνηση για τη νόσο Creutzfeldt-Jakob (CJD) με αναζήτηση πρωτεΐνης 14-3-3 και

RT-QuIC assay,οι οποίες ήταν εντόνως θετικές. Στην ανάλυση κυτταρομετρίας ροής του εγκεφαλονωτιαίου υγρού ανευρέθη αυξημένος πληθυσμός Τ-κυττάρων, ενδεικτικός για λέμφωμα του ΚΝΣ. Πραγματοποιήθηκε βιοψία εγκεφάλου, η οποία ανέδειξε διήθηση του εγκεφάλου από ένα κακοήθες Τ-κυτταρικό λέμφωμα, πιθανώς στα πλαίσια μετατροπής μεγάλων κυττάρων της σπογγοειδούς μυκητίασης με έκφραση CD30. Από νευρολογικής πλευράς η θεραπεία με ώσεις στεροειδών έδρασε αρχικά θετικά στην αφύπνιση και την αποδρομή των συγχυτικών επεισοδίων.Ακολούθησε ογκολογική αντιμετώπιση. **Συμπέρασμα:** Η θετική δοκιμασία RT-QuIC συνδέεται στενά με τη CJD, με ειδικότητα που φθάνει το 99%. Στην βιβλιογραφία είναι σπάνια τα περιστατικά θετικοποίησης της δοκιμασίας σε άλλα αίτια όπως στο λέμφωμα του ΚΝΣ, γεγονός που προσδίδει ενδιαφέρον στην προσέγγιση των υποξέων εγκεφαλοπαθειών.

Λέξεις-κλειδιά: σπογγοειδής μυκητίαση, RT-QuIC, λέμφωμα Τ-κυττάρων

INTRODUCTION

Sporadic Creutzfeldt-Jakob disease (sCJD), characterised by rapidly progressive neurodegeneration, represents the most common form of human prion disease, with mean survival ranging from 4 to 12 months.[1] Early clinical manifestations include cognitive impairment with cerebellar signs, constitutional symptoms, behavioural disturbance, and less commonly corticospinal and extrapyramidal signs, which can resemble those of other non-prion diseases.[2] Seizures and acute onset of consciousness disturbance are reported, but infrequent. Typical MRI findings comprise of cortical ribboning in at least two cortical regions and basal ganglia signal changes, whilst EEG can range from non-specific findings such as diffuse slowing in early stages to typical periodic sharp wave complexes later in the course of the disease.[1,3]

Diagnosis of CJD encompasses clinical signs, neuroimaging and EEG changes, and is usually validated by CSF analysis.[4] The real-time quaking-induced conversion (RT-QuIC) assay detects prion-seeded amyloid fibril formation by recombinant prion protein. Recent research has substantiated the high sensitivity (85%) and specificity (99%) of RT-QuIC in CSF for the diagnosis of prion diseases.[4,5] While a small number of cases with potential false-positive outcomes have been documented, these reports lack comprehensive pathological information.[6]

In this context, we hereby present a rare case of CNS involvement in mycosis fungoides, a type of cutaneous T-cell lymphoma, with large cell transformation with positive RT-QuIC assay result. This case underscores the significance of conducting a comprehensive evaluation and confirming the diagnosis through pathological analysis when interpreting RT-QuIC results in patients with suspected prion diseases.

CASE PRESENTATION

A 73-year-old, previously independent, Caucasian man presented to the ER with status epilepticus. Despite immediate medical management, he required emergency intubation with ventilatory support and observation in ICU. The patient had a past medical history of mycosis fungoides, which had been diagnosed three years previously and managed with PUVA therapy. During follow-up there was no systemic involvement of the disease detected. There was no remarkable family history of neurological diseases and there were no previous neurological symptoms reported.

The patient underwent a CT scan of the head right after intubation, which reported some non-specific white matter hypodensities bilaterally. A lumbar puncture was then performed, which revealed lymphocytic pleocytosis and increased CSF protein levels. The patient was empirically treated with intravenous acyclovir, since viral encephalitis was the principal differential diagnosis. The negative antiviral PCR panel in CSF analysis prompted exploration of other possible differential diagnoses, such as autoimmune encephalitides. A course of intravenous steroids was therefore initiated. The patient was successfully extubated ten days later. Over the course of the following days, he exhibited a fluctuating level of consciousness along with cognitive deficits in the form of memory impairment and disorientation. Subsequently, an MR scan of the brain was performed, which revealed multiple hyperintense lesions in the right frontotemporal region, bilateral insula and right anterior corona radiata, some of which demonstrated contrast enhancement (**Figure 1**). CSF flow cytometry reported increased number of T-lymphocytes with CD7 and CD117 single positivity.

After steroid therapy tapering and subsequent withdrawal, new focal epileptic seizures were observed. A further lumbar puncture was performed. The CSF was acellular with negative paraneoplastic and autoimmune markers. The patient received a second course of pulsed intravenous methylprednisolone. Paraneoplastic and autoimmune encephalitis antibodies in the CSF and serum were negative, however, CSF analysis reported positive results for 14-3-3 protein and RT-QuIC.

Clinical improvement was achieved after steroid therapy in context of the level of consciousness, but continued to exhibit cognitive impairment. On se-

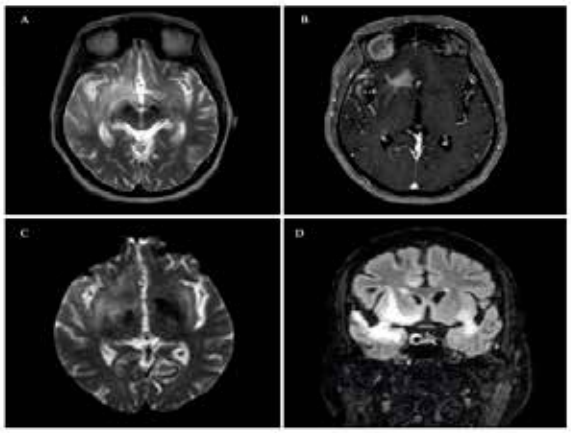

Figure 1. Initial MRI scans of the brain. (a) Axial T2 showing high signal in the right temporal lobe. (b) Axial post-contrast scan, demonstrating an area of contrast enhancement in the right temporal lobe. (c) Axial DWI, depicting a similar area of high signal in the right temporal lobe. (d) Coronal FLAIR with high signal in both temporal lobes and extending to basal ganglia bilaterally.

rial MR scans of the brain, the hyperintense lesions were found slightly decreased in size, but continued to exhibit contrast enhancement. A bone marrow biopsy was carried out in view of the positive immunophenotyping results, but did not detect lymphoma infiltration. On serial EEGs, there was evidence of encephalopathic changes, but no epileptiform activity was observed.

The positive 14-3-3 and RT-QuIC results, in conjunction with the rapid cognitive decline and encephalopathy would support the diagnosis of CJD. The patient fulfilled the CDC diagnostic criteria for probable prion disease.[1] However, there was absence of other neurological signs pointing towards this diagnosis, such as akinetic mutism, cerebellar signs or myoclonus, as well as absence of periodic sharp-wave complexes in serial EEGs, considered typical for the disease or typical neuroimaging findings. A subsequent lumbar puncture performed during steroid therapy revealed decreased levels of 14-3-3, positive RT-QuIC and negative flow cytometry for lymphoma. Due to differential diagnosis ambivalence, a brain biopsy was considered. The latter revealed infiltration of brain tissue by a highly malignant T-cell lymphoma of T-cell origin with intense CD30 expression most likely in the context of large cell transformation spongiform mycosis with CD30 expression (**Figure 2**). The patient was treated for invasive CNS lymphoma with 2 cycles of methotrexate, then cytarabine and brentuximab, but did not sufficiently respond to the treatment and passed away a few months later.

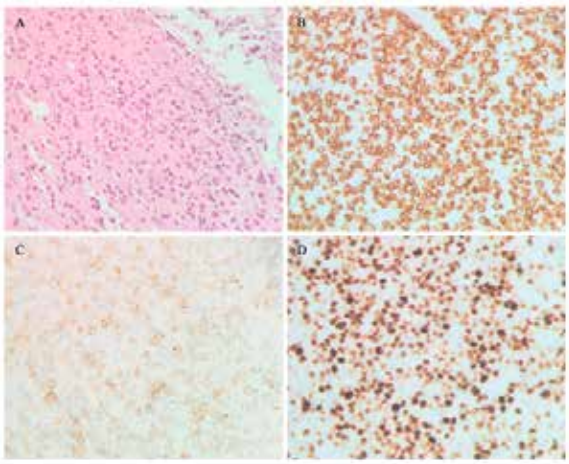

Figure 2. Histological images from the patient's brain biopsy. **(a)** Infiltration of brain parenchyma by medium-sized lymphocytes with dark chromatin and irregular nuclear membrane (Haematoxylin and eosin x400 magnification). **(b)** CD3 expression in medium-sized lymphocytes (IHC x400 magnification). **(c)** CD30 expression in most lymphocytes (IHC x200 magnification). **(d)** Ki-67 expression in the majority of neoplastic lymphocytes (IHC x400 magnification).
IHC: immunochemistry.

DISCUSSION

RT-QuIC assay has been relatively recently added to the diagnostic tests for CJD. Its high sensitivity and specificity render it invaluable for prion disease detection; it has now been added as a component of the diagnostic criteria for CJD.[1] It is able to accurately detect the pathogenic agent (PrP^{Sc}), identified to be responsible for CJD occurrence.[4] The high specificity of RT-QuIC for prion detection is achieved through a lengthy process in which the binding of PrP^{Sc} in the CSF to a mixture of recombinant PrP and thioflavin T is tracked in real time, as the presence of PrP^{Sc} causes fluorescence of the agglomerates formed.[7] RT-QuIC assay appears to be more sensitive and more specific compared to 14-3-3 protein detection, the latter yielding a false-positive rate of 0.098 according to a meta-analysis of 2500 patients, and known to give a false-positive result in cases of neurodegeneration and possibly neuroinflammation.[8] The same meta-analysis reported no false-positive results for RT-QuIC assay.[8] Thus far, there have only been a few cases of RT-QuIC false-positive results reported in literature, in the context of unrelated to prion neurodegeneration and none related to CNS malignant processes.[6] As is the case with all diagnostic immunological assays, RT-QuIC should be interpreted carefully, taking into account the broader clinical presentation, and serving as an adjunct to the clinical signs, examination and other investigations. It would have been of benefit to determine if RT-QuIC and 14-3-3 results turned negative after chemotherapy, but the poor medical state and subsequent death of the patient precluded further investigations. It has been disputed that high white cell count in CSF as well as

high levels of total protein might account for a false positive RT-QuIC response,[7] although infrequently CJD patients demonstrate the above findings.[9] In our case, RT-QuIC remained positive even after an acellular lumbar puncture.

Mycosis fungoides is the most common form of cutaneous T-cell lymphoma.[10] CNS involvement in mycosis fungoides is uncommon, with case-series reporting less than 2% of total patients studied experiencing CNS attack.[11] However, it has been suggested that subclinical involvement rates are higher, as shown in older post-mortem studies. It is estimated that spread of the disease to the CNS might occur within a median time of 5.4 years from diagnosis.[12] Disease with CNS involvement carries a poor prognosis, with a few months of predicted survival time in treated or untreated cases.[11,12] Clinical presentation can largely vary, depending heavily on the location of the injury. Although meningeal disease with leptomeningeal enhancement on post-contrast MRI is more common, cases of contrast-enhancing parenchymal lesions have been reported.[12] Treatment options include various combinations of chemotherapy medications and temozolamide.[12] More recently, radiotherapy has been used with some promising results, although more research has to be conducted on this field.[13]

CONCLUSION

We would hereby like to underline the rare likelihood of positive RT-QuIC assay results on a patient with a biopsy-verified CNS T-cell lymphoma, as demonstrated in two separate CSF samples. The role of RT-QuIC as a laboratory tool of CNS lymphoma diagnosis is at present unchallenged. However, the possibility of coexistence of subclinical CJD has not been excluded. In literature, there has only been one case of coexistence of a brain tumour, a vestibular schwannoma and CJD.[14] This case highlights the significance of pathological confirmation, including western-blot analysis, particularly in complex diagnostic cases where multiple potential aetiologies need to be considered.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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