Diagnostic challenges in a patient with Progressive Encephalopathy and MRI changes after allogeneic HSCT and immunosuppression: a case report.

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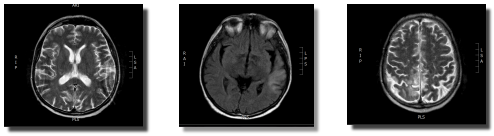
Introduction:
Neurologic disorders in patients with haematologic malignancies and allogeneic haematopoietic stem cell transplantation (HSCT) represent a significant diagnostic challenge. Causes can range from recurrences to infectious/post-infectious diseases, drug-induced toxicity, or GVHD. Identifying appropriate diagnosis is paramount in view of substantially different courses of action and therapeutic possibilities.

Case presentation:
A 49 y.o. male past history was notable for Acute Lymphocytic Leukemia for which he received induction chemotherapy and Hematopoietic Stem Cell Transplantation. Although he reached complete remission from the haematologic malignancy, HSCT was complicated by frequent CMV reactivations and pulmonary graft vs host disease, reason for which he started immunosuppresive treatment with Rapamune (Sirolimus) and Prednisone (time from HSCT: 16 months).
On day 65 after treatment with Sirolimus had begun he presented to our Department of Neurology.

Clinical features were: mild expressive aphasia, left ataxic hemiparesis with ataxic gait, diffuse hyperreflexia with right ankle clonus.

First brain MRI showed widespread and bilateral areas of alteration of signal (hypointense in T1-weighted and hyperintense in T2-weighted images). Lesions were devoid of oedema, contrast enhancement or mass effect.

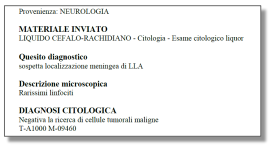


Differential diagnosis included the following:

- Progressive Multifocal Leukoencephalopathy
- Meningeal involvement by the ALL
- Neurological manifestation of GVHD
- Sirolimus-induced reversible leukoencephalopathy syndrome

In agreement with the consultant haematologist Sirolimus was withdrawn, and Prednisone gradually tapered.

Two repeated lumbar punctures were performed (in two weeks distance one from each other): in both, CFS analysis was unremarkable and research for malignant cells resulted negative (ruling out meningeal involvement by ALL).
In addition, **qualitative and quantitative PCR assays for JC virus DNA yielded negative results.**
Concurrently, Neurological assessment revealed slight worsening of aphasia and gait disturbance, second MRI cerebral study (performed 6 weeks after the first) confirmed progression of lesions. This finding made diagnosis of drug-induced encephalopathy unlikely and was, on the other hand, **strongly suggestive of PML.**

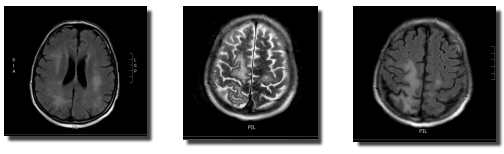

Provenienza: NEUROLOGIA

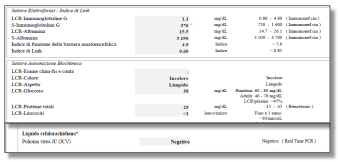
MATERIALE INVIATO
LIQUIDO CEFALO-RACHIDIANO - Citologia - Esame citologico liquor

Quesito diagnostico
sospetta localizzazione meningea di LLA

Descrizione microscopica
Rarissimi linfociti

DIAGNOSI CITOLOGICA
Negativa la ricerca di cellule tumorali maligne
T-A1000 M-09460





Today: after 5 months of physical rehabilitation and treatment with Mirtazapine 30 mg daily, patient has mild left hemiparesis with good control of left hand, fluent speech and autonomous maintenance of standing position. Next brain MRI is scheduled on 3/10.

Conclusion:
It must be kept in mind that JCV DNA may be undetectable in the CSF in up to 22.7% of cases. In view of this fact, at least for the time being, **a clinical-radiological diagnosis of PML can be made**; although for definite diagnosis more sensitive tests and especially a brain biopsy should be required.
This case highlights some of the diagnostic and therapeutic challenges in haematologic patients and is, to the best of our knowledge, the first report of possible PML in this setting.

Bibliography:
- Oliver Grauer, Daniel Wolff, Hartmut Bertz, Hildegard Greinix, Jorn-Sven, Kuhl Anita, Lawitschka Stephanie, J. Lee Steven, Z. Pavletic, Ernst Holler, Ingo Kleiter. Neurological manifestations of chronic graft-versus-host disease after allogeneic haematopoietic stem cell transplantation: report from the Consensus Conference on Clinical Practice in chronic graft-versus-host disease. *Brain 2010; 133 (10): 2852-2865*
- Maas RP, Muller-Hansma AH, Esselink RA, Murk JL, Warnke C, Killestein J, Wattjes MP. Drug-associated progressive multifocal leukoencephalopathy: a clinical, radiological, and cerebrospinal fluid analysis of 326 cases. *J Neurol. 2016 Oct;263(10):2004-21*
- A Moskowitz· C Nolan, E Lis, H Castro-Malaspina· M-A Perales. Posterior reversible encephalopathy syndrome due to sirolimus. *Bone Marrow Transplantation* 2007; 39, 653–6540