Nocardia abscesses mimicking tumor progression in gliomatosis cerebri responding to temozolomide

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To the Editor,

Gliomatosiscerebri (GC) is a diffuse grade III glioma according to WHO 2007which is increasingly treated with upfront chemotherapy [1-2].Nocardiabrain abscesses are rare, about 2% of all brain abscesses, and often occur in immunodeficient patients, such as those receiving chemotherapy and steroids [3]. We present the case of a patient with GC responding to temozolomide, who developed Nocardia brain abscesses within the neoplastic lesion. We discuss the specific diagnostic challenges in terms of differential diagnosis and treatment.

Case report.

A 68 year-old male presented with a generalized tonic-clonic seizure.Patient had developed headache and vertigo over the previous two months while the prior medical history was unremarkable. MRI showed a diffuse hyperintense lesion in FLAIR sequencesinvolving the right temporal, parietal and occipital lobes and extending into the left hemisphere and the cerebellum(Fig. 1a). No contrast enhancement was observed. An open biopsy was performed and histology showed a neoplastic astrocytic proliferation, consistent withgliomatosiscerebri(Fig 1b). The patient receiveddose-dense temozolomide (150 mg/m2/day 1 week on/1 week off) and a partial responsewas observed on T2/FLAIR images according to RANO criteria (Fig. 1c), with an improvement of neurological symptoms. The patient was off steroids since the beginning of chemotherapy, but he developed a progressive lymphopenia (gr. 2, CTCAE v4.0).

After 14 cycles, the patient developedan intense headache with neck pain, nausea, vomiting, vertigo with right beating nystagmus and VI and VII cranial nerve impairment. He

had no fever and blood tests confirmed the lymphopenia with decreased T helper cells count (lymphocytes: 0.7 10^9/L, CD4+ lymphocytes: 0.09 10^9/L), without an increase of neutrophils count or other inflammatory markers. MRI revealed two ring-shaped contrast enhancing lesions in the right temporo-parietal junction and right cerebellar hemisphere (Fig. 1d), i.e. within the preexistent neoplasia. The new lesions were intensely hyperintense in diffusion; MR spectroscopy and perfusion showed an increase of the choline peak and choline/NAA ratio in the enhancing areas, without an increase of rCBV. The lesions tended to increase in size over the following two weeks. Chest CT demonstrated apericardiac opacity in the left lung and few homolateraladenopathies. Whole body FDG PET demonstrated an increased uptake of the cerebellar and lung lesions. Tumor markers were negative. Differential diagnosis included a malignant transformation of the preexistent GC, metastases of a lung cancer or multiple infective abscesses.

A fine-needle biopsy of the lung lesionrevealed a non-specific inflammation without neoplastic cells. Due to the rapid neurological deterioration, surgical resection of the cerebellar lesion was performed. The histological examination showed an intense neutrophilic, inflammatory infiltrate with areas of necrosis and ofincreased astrocytic cellularity, while theGrocott'smethenamine silver staining showedbacteria with morphology consistent withNocardiaspecies and the diagnosis was later confirmed by culture tests (Fig. 1e).

Antibiotic treatment with intravenous trimethoprim/sulfamethoxazole (TMP-SMX) and ceftriaxone was started,yielding a neurological improvement in the following weeks, and a reduction in size of brain and lung lesions. After 6 months of maintenance treatment with oral TMP-SMX the patient recovered completely and MRI showed a near-total

disappearance of lesions without an evidence of GC progression (Fig. 1f). The patient is still alive3 years from the initial diagnosis, free from progression without further treatments.

Discussion.

At our knowledge, this is the first case of agliomatosiscerebri patient with a long lasting response to temozolomidein whom an opportunistic infection, probably related to the chemotherapy-induced immunosuppression, developed at the preexistent tumor site, thus mimicking a malignant transformation.

Neuroimaging findings were not conclusive. The lack of systemic symptomsand the rapid increase of lesions favored the hypothesis of a GC progression, but on the other hand, lymphopeniawith low CD4+ lymphocytes count, typical of a dose-dense regimen of temozolomide, was a risk factor for developing anopportunistic infection.

In conclusion, a neurological deterioration in patients with malignant gliomas responding to chemotherapy can rarely be due to treatable non-neoplasticcauses. This case shows the importance of obtaining an histological confirmation whentumor progression is suspected, but clinical and neuroimaging findings are equivocal.

Figure title and caption

Fig. 1 Radiological and histological features of the gliomatosiscerebri and the Nocardia brain abscesses. (a)Axial FLAIR MRI at initial presentation: extensive hyperintense lesion involving the right temporal, parietal and occipital lobes, extending into the left hemisphere and the cerebellum without contrast enhancement; (b)H&E stain: increased astrocytic cellularity consistent with a diagnosis of gliomatosiscerebri according to WHO 2007; (c)Axial FLAIR MRI after 12 cycles of chemotherapy: partial response according to RANO criteria; (d)T1-weighted with gadolinium MRI at the end of 14^{th} cycle of chemotherapy after admittance because of clinical worsening: ring-shaped contrast-enhancing lesions at the right temporo-parietal junction and in the right cerebellar hemisphere; (e)Grocott'smethenamine silver stain: bacterial infiltrate consistent with Nocardia species; (f)T1-weighted with gadolinium MRI after 6 month of maintenance therapy with TMP-SMX: near-total disappearance of the lesions.

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