

Respuesta a vismodegib en un meduloblastoma recurrente

Response to vismodegib in recurrent medulloblastoma

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A 32 year-old female patient was seen in 2006 suffering from headaches, vertical diplopia and a gradually-developing unsteady gait. CT scan revealed a 40 x 40 mm intra-axial cerebellar mass affecting the vermis. She underwent gross total resection with histology being compatible with a primitive neuro-ectodermal pattern. The final report was consistent with a desmoplastic nodular medulloblastoma (WHO grade IV), 20% Ki67, with focal reactivity for synaptophysin, neurofilaments and CD99. Bone marrow biopsy and cerebrospinal fluid were negative. She received adjuvant craniospinal radiotherapy, followed by chemotherapy with cyclophosphamide, cisplatin, etoposide and vincristine which was well-tolerated. She was then closely followed-up for 5 years with no evidence of relapse until an MRI then identified a new lesion within the posterior fossa which was biopsied and confirmed recurrent disease. She was evaluated at MD Anderson Cancer Center (MDACC) and in conjunction with our oncology department we decided to treat her with induction chemotherapy involving cyclophosphamide, cisplatin and etoposide. After 6 cycles she underwent to intensified dose therapy (carboplatin, thiotepa and etoposide) achieving a complete response. Eleven-month postoperative MRI indicated tumour relapse which was confirmed by PET/CT whilst complimentary 14-month imaging revealed leptomeningeal infiltration (figure 1). This was initially treated with gamma-knife radiosurgery, followed by one dose of bevacizumab. She tested positive for SHH with PATCHed-1 activation by immunohistochemistry; after this result we switch to 150 mg/day vismodegib and the MRI revealed partial response after two months' treatment (figure 2). Her symptoms improved as well as her neurological exam.

Medulloblastomas (MB) are primary malignant embryonic tumours affecting the central nervous

system (CNS). They are the most common CNS tumour in the paediatric population, but are very rare in the adult population (0,5 per million reported incidence), accounting for less than 1% of primary brain tumours in young adults¹. Clinical features include truncal ataxia, gait disturbances and symptoms arising from increased intracranial pressure (headache, vomiting). Most originate within the posterior fossa, sometimes infiltrating across the ependymal lining into the brainstem or disseminating within central spinal fluid. Most information regarding its treatment is extrapolated from paediatric data or is based on retrospective reviews. Patients having recurrent disease after primary therapy have a particularly poor prognosis, mean survival rate (SR) being less than 6 months, 9% having a 2-year SR². Second line therapy is limited. Genome-wide sequencing has identified four distinct molecular subtypes: the wingless signalling (WNT) and sonic hedgehog pathway-activated groups (SHH), group 3 and group 4; SHH is the most common subtype, accounting for 60% to 80% of all adult MB. These medulloblastomas are often desmoplastic³.

The hedgehog signalling pathway is an embryonic signalling cascade which regulates stem cell differentiation; it is activated by transmembrane protein smoothed (SMO) signalling; the protein patched homologue 1 (PTCH1), sonic hedgehog receptor, suppresses hedgehog pathway activation by inhibiting SMO. SHH binding to PTCH1 results in inactivation of PTCH1, thereby limiting SMO inhibition and promoting pathway activation^{2,4,5}. Mutations resulting in SHH over-activation are thus critical in the pathogenesis of various malignancies, including MB, providing an opportunity for targeted therapy. Cyclopamine (Veratrum alkaloid) was the first agent discovered to be able to disrupt this pathway by binding to SMO^{6,7}, demonstrating *in vitro* and *in vivo* inhibition

of tumour growth. This finding triggered active research into developing other SMO inhibitors.

The first results in humans demonstrating a response to the SMO inhibitor (GDC-0449) were published in 2009; a phase I clinical trial reported an acceptable safety profile and encouraging anti-tumour activity in advanced basal cell carcinoma (BCC) and MB⁸. Rapid tumour regression was seen in metastatic MB². Such trials culminated in recent FDA approval of vismodegib for BCC in January 2012. Although trials are still ongoing, SMO inhibitors seem promising regarding MB. Phase II trial results evaluating vismodegib efficacy and safety in adult patients suffering recurrent or refractory MB medulloblastoma have been presented recently. Thirty-two patients having measurable disease were

treated with vismodegib. No response was observed in non-SHH tumours. Three out of twenty patients having SHH tumours had a sustained response (maintained for at least 8 weeks). Mean therapy duration was 2,76 months; some patients remained on treatment for up to 13 months. The most common toxicity was grade 3 decrease in lymphocytes, myalgia, seizures, back pain and syncope, presented by 4 patients during a first course and 3 patients during a second one. One patient experienced a grade 4 thromboembolic event. These results demonstrated vismodegib activity and security concerning recurrent or refractory SHH subtype medulloblastoma⁹. At least 7 additional SMO antagonists are currently being developed in various stages of clinical trial¹⁰.

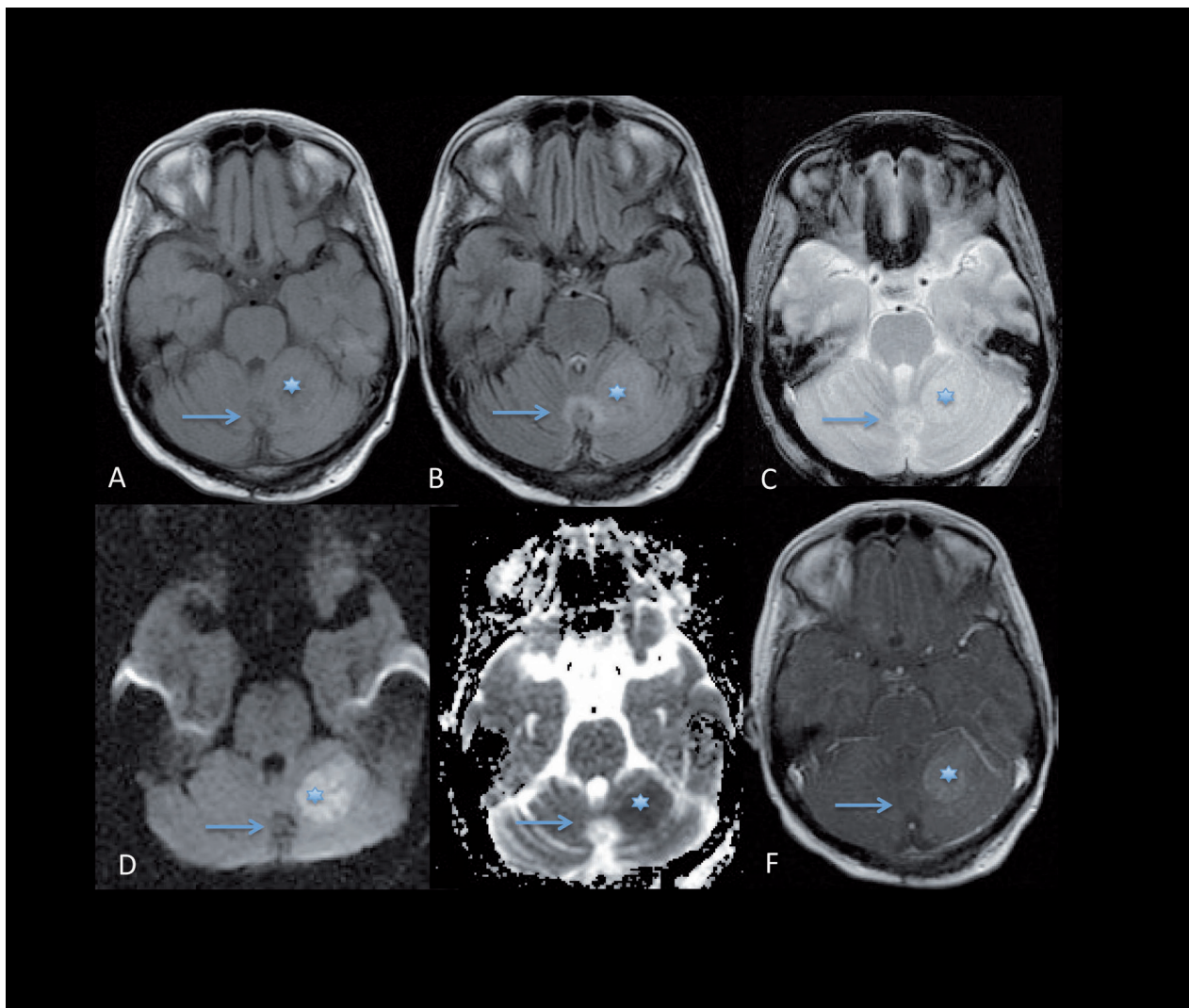


Figure 1. Simple and contrast magnetic resonance of the brain at the moment of relapse (2011).

A. T1W B. FLAIR C. GRE T2 D. DWI E. ADC F. T1W contrast

Axial cross-sections showing post-surgery encephalomalacia and gliosis in the vermis (arrow) and left cerebellum nodular lesion, revealed with contrast, without bleeding and with restriction of diffusion, showing tumour recurrence (*).

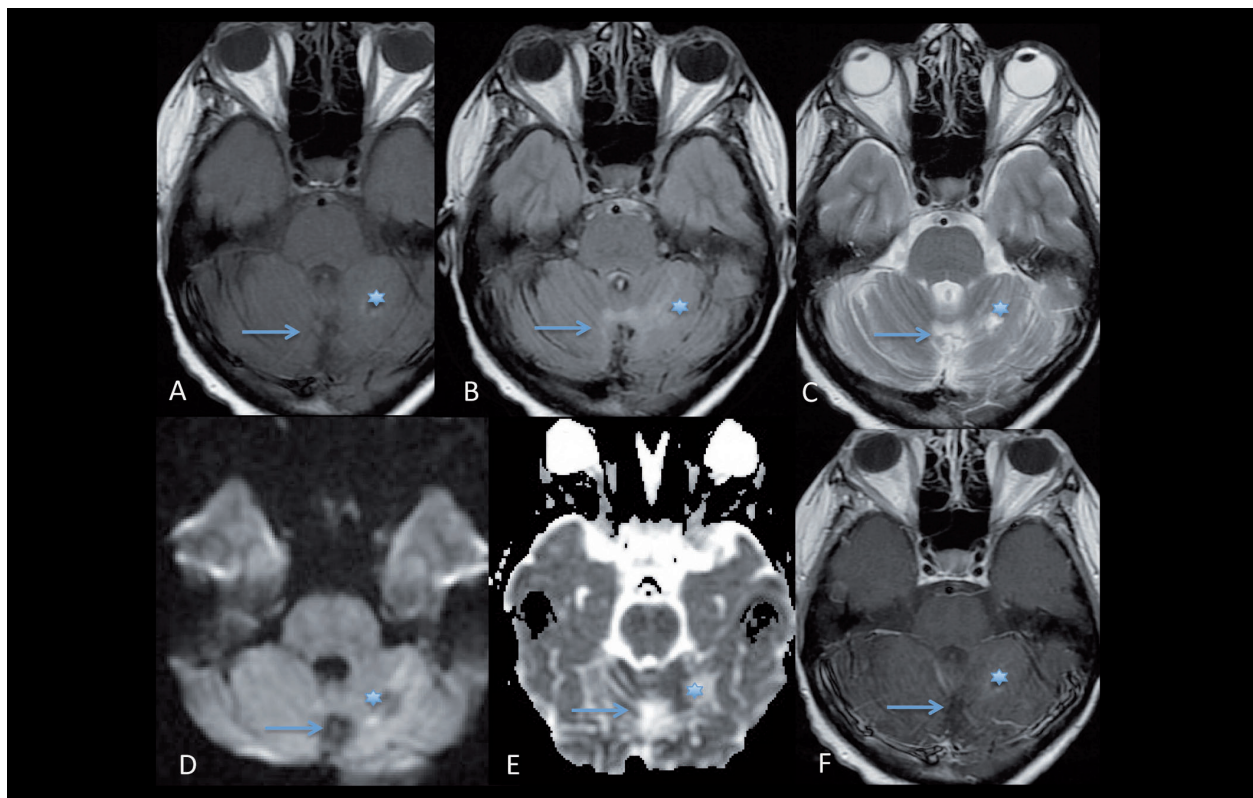


Figure 2. Simple and contrast magnetic resonance of the brain 6 months after high dose chemotherapy plus peripheral blood stem cell rescue (2012).

A. T1W B. FLAIR C. T2W D. DWI E. ADC F. T1W contrast

Axial cross-sections showing post-surgery encephalomalacy and gliosis in the vermis (arrow) and in the left cerebellar hemisphere showing evidence of nodular lesion, without signs of residual tumour (*).

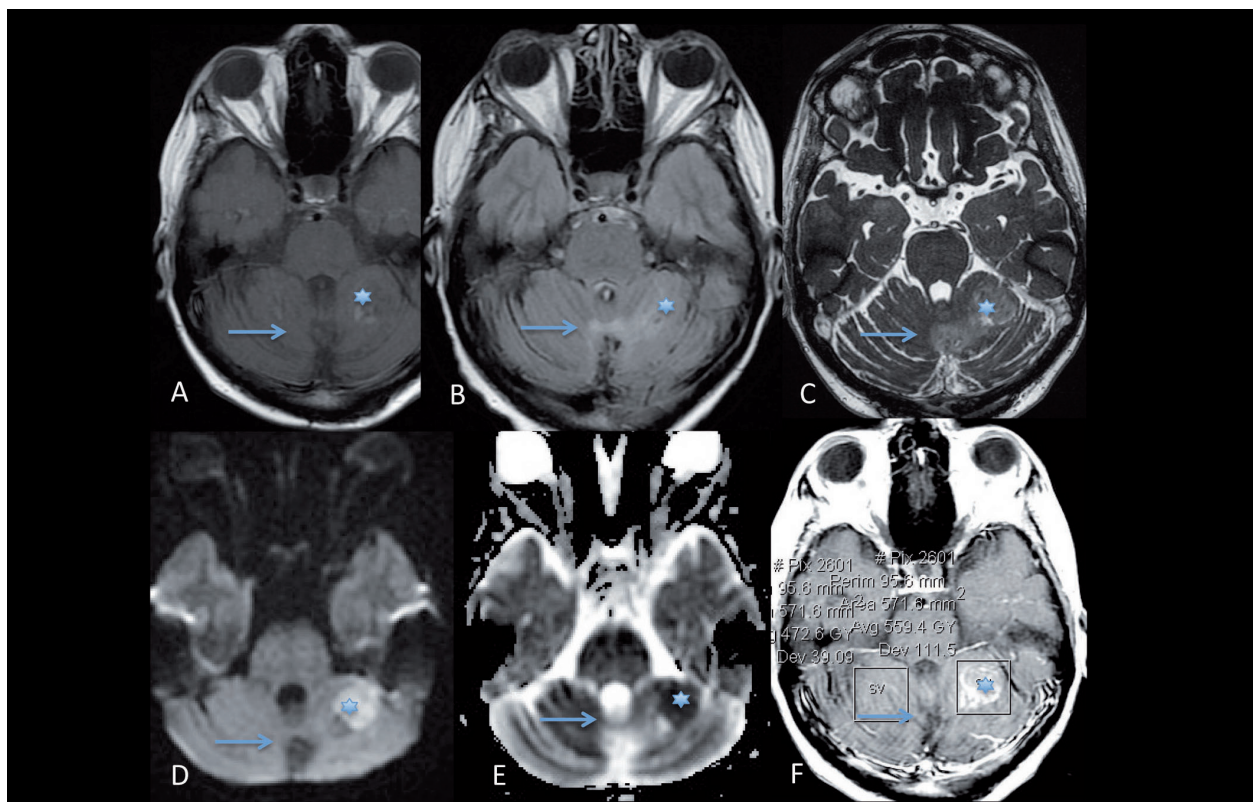


Figure 3. Simple and contrast magnetic resonance of the brain following stem cell transplantation showing focal relapse (treated with radiosurgery).

A. T1W B. FLAIR C. T2W D. DWI E. ADC F. T1W contrast

Axial cross-sections showing post-surgery encephalomalacy and gliosis in the vermis (arrow) and signs of a fresh tumour relapse in the left cerebellar hemisphere (*).

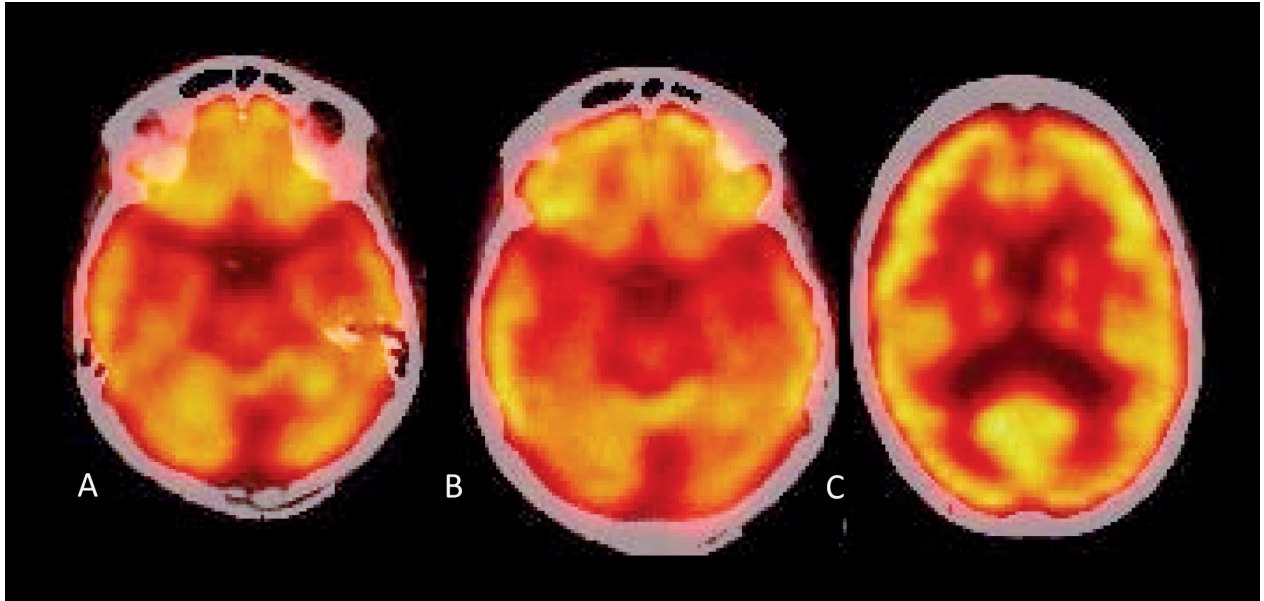


Figure 4. FDG/PET 9 months after stem cell transplantation showing a focal tumour relapse (treated with radiosurgery).
A, B, C. PET post-transplant with signs of hyper-metabolic lesion corresponding to tumour relapse.

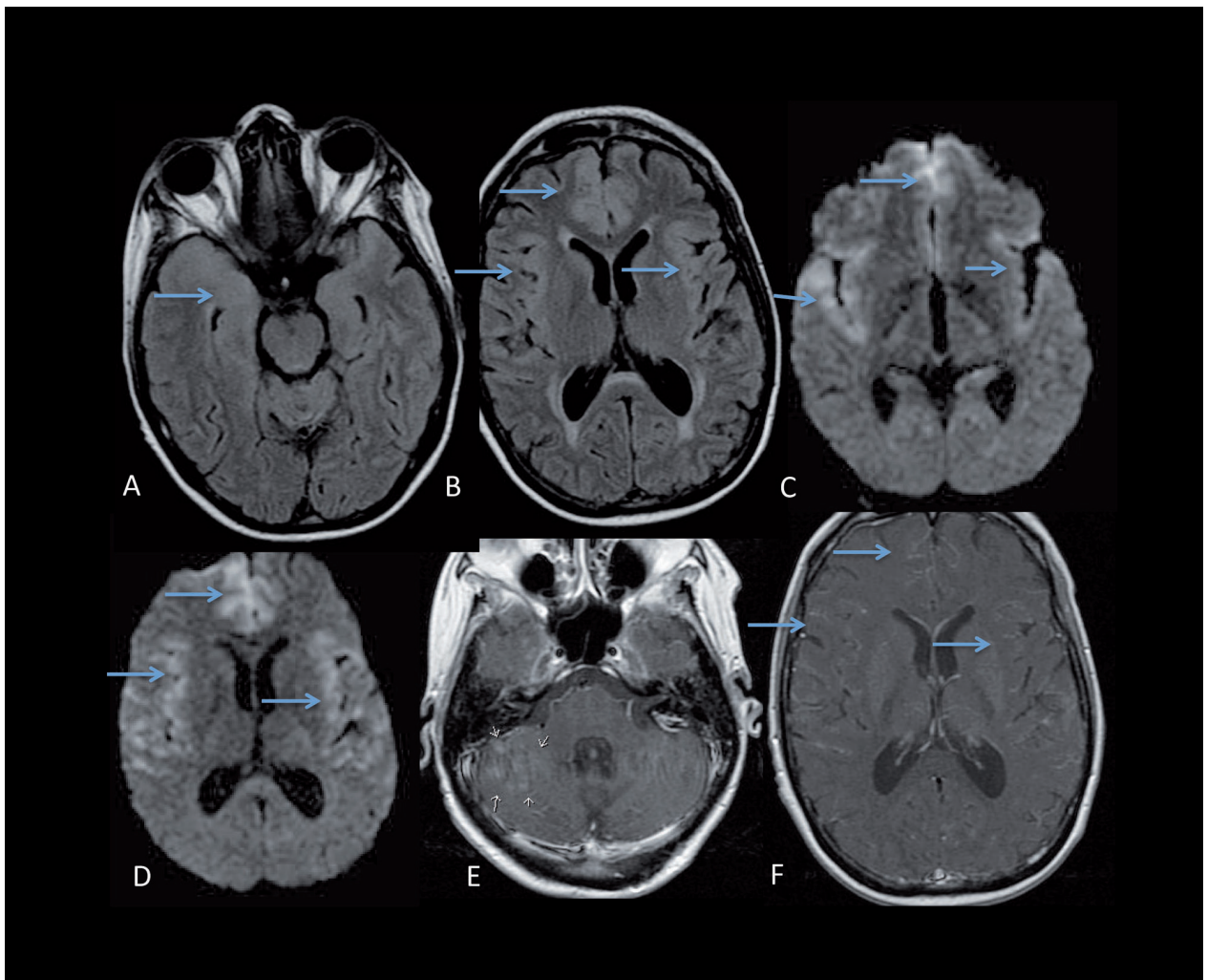


Figure 5. Simple and contrast magnetic resonance of the brain 4 months after radiosurgery, showing leptomeningeal metastatic lesions.
A. FLAIR B. FLAIR C. DWI D. DWI E. T1W contrast F. T1W contrast
Axial cross-sections showing areas of signal alteration, with áreas of altered difusión similar to that observed in the initial relapse done with contrast (arrow).

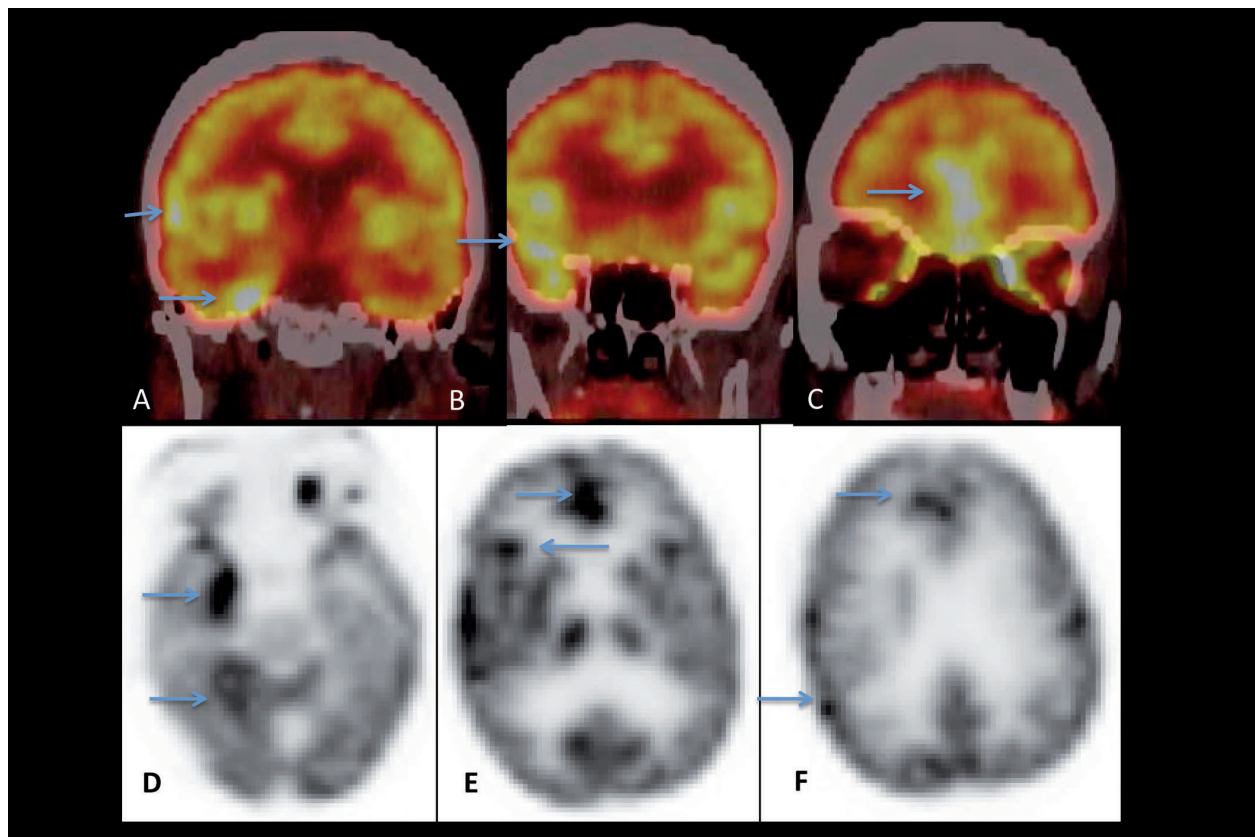


Figure 6. PET-FDG post-radiosurgery with metastatic lesions. Coronal and axial cross-sections showing areas of increased metabolism (arrows) consistent with leptomeningeal dissemination.

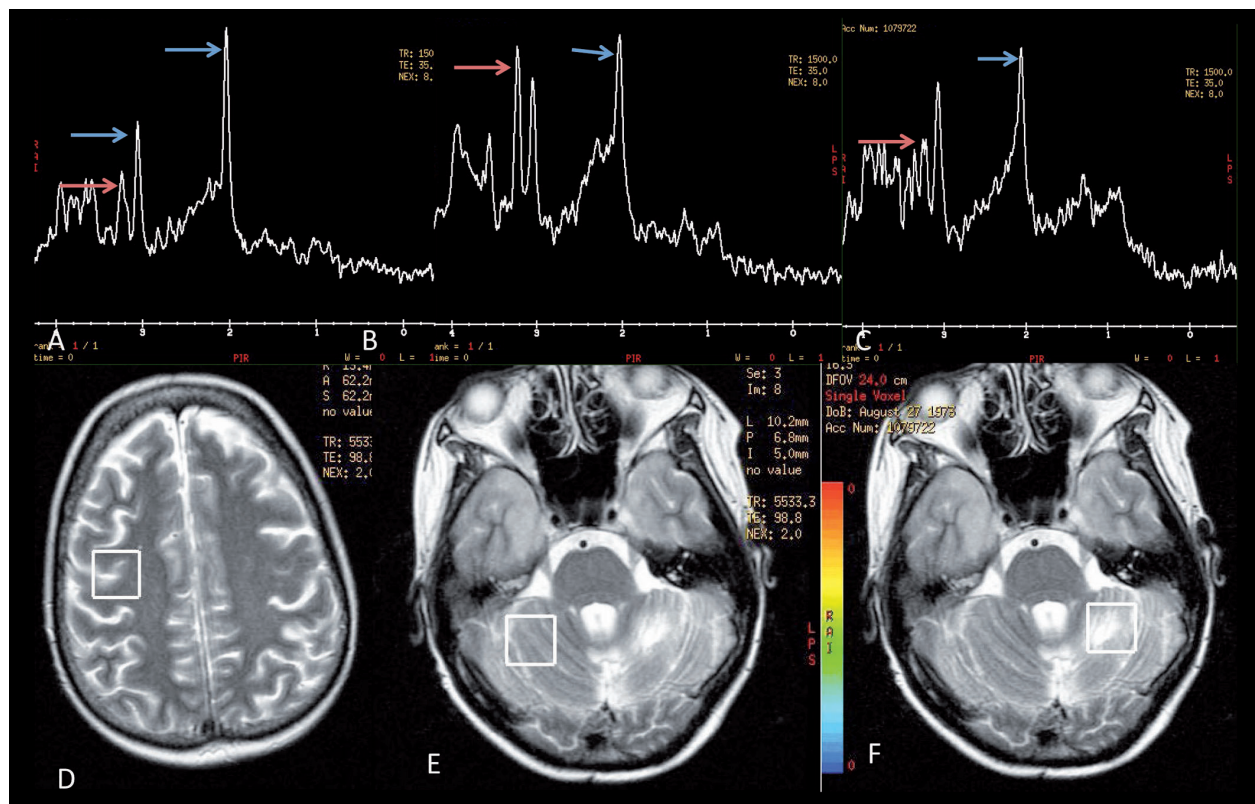


Figure 7. MR spectroscopy showing the respective choline (Cho), creatine (Cr) and N acetyl aspartate (NAA) peaks in D, E and F (where voxels were taken) and in A, B and C. A and D show normal tissue with high NAA peak (blue arrow) and the expected height for Cho (red arrow) and Cr peaks. B and E show high Cho peak and a drop in NAA showing tumour tissue. C and F show a drop in both peaks, probably due to post-treatment changes.

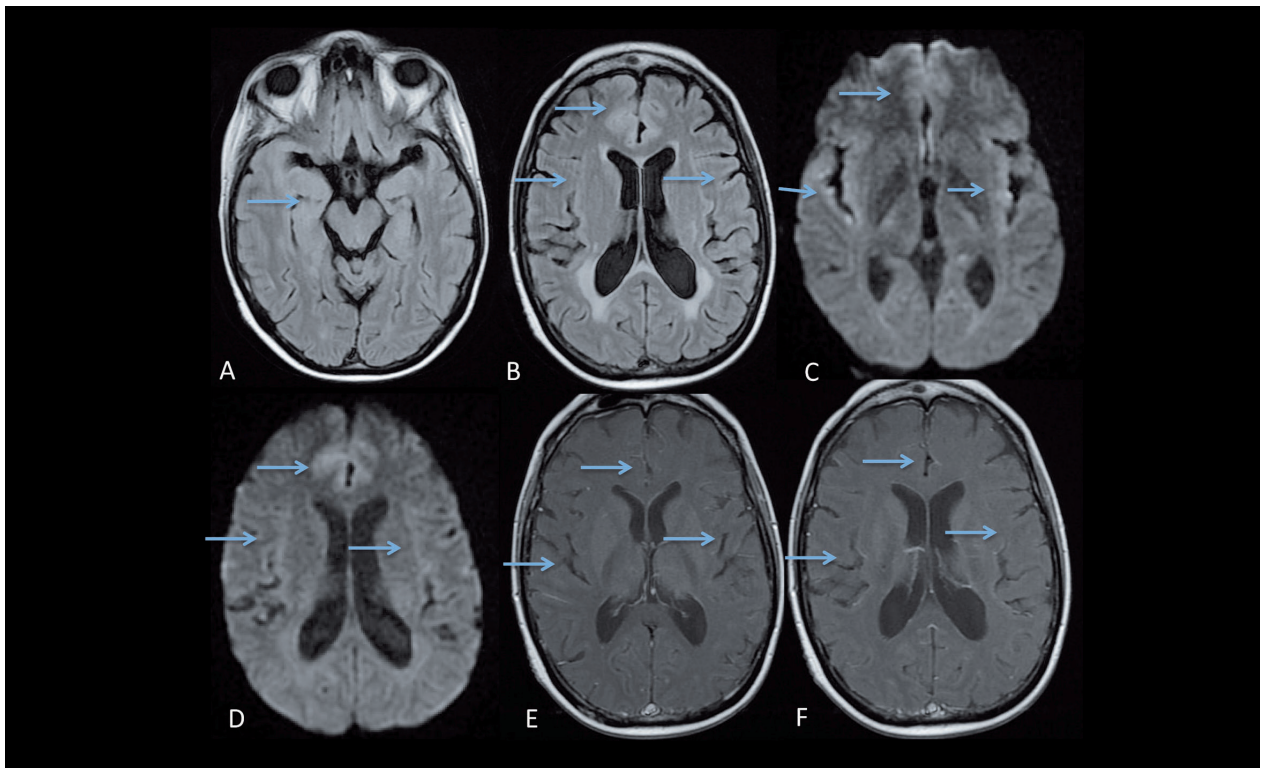


Figure 8. Simple and contrast MR of the brain 4 weeks after starting vismodegib.

A. FLAIR B. FLAIR C. DWI D. DWI E. T1W contrast F. T1W contrast

Axial cross-sections showing reduced size of areas of signal alteration, with reduced alteration regarding (almost complete) disappearance of diffusion done with contrast (arrows).

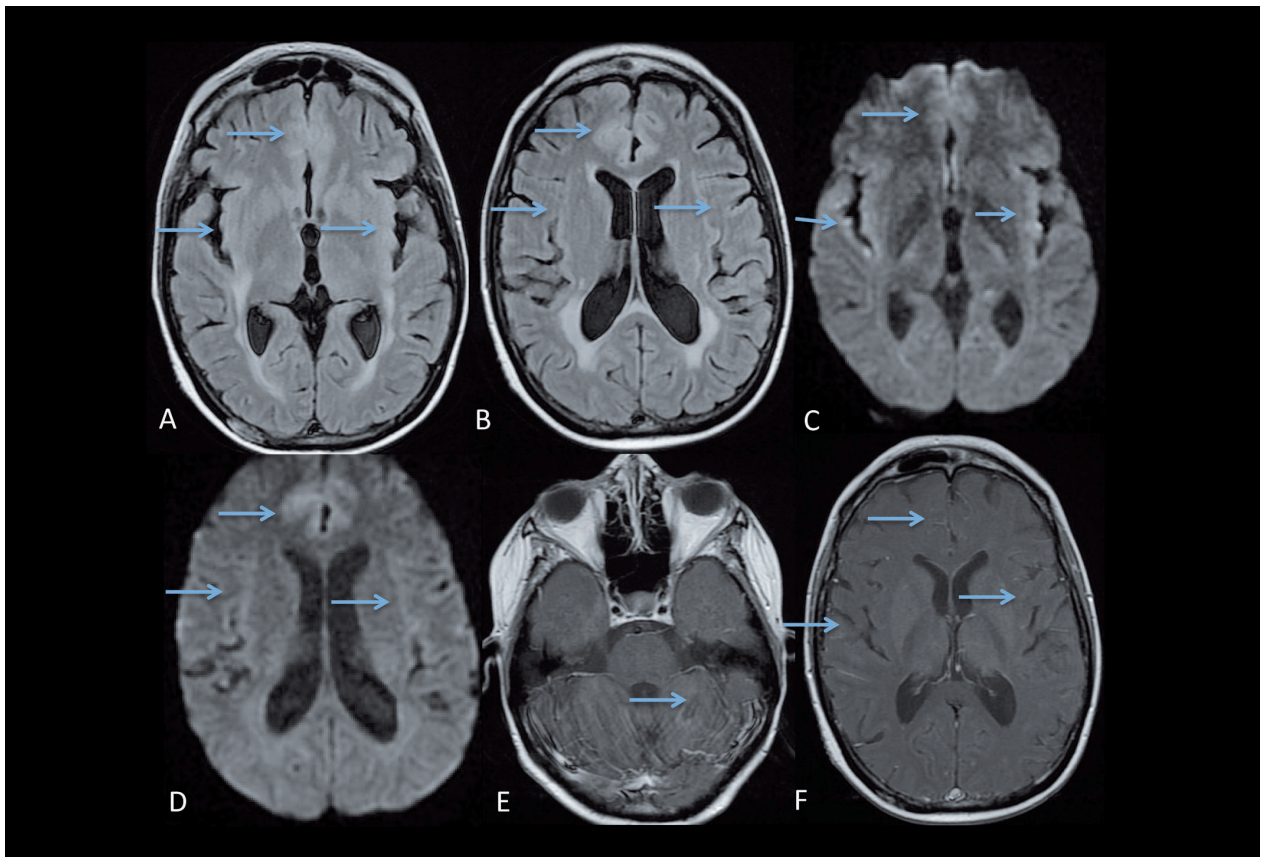


Figure 9. Simple and contrast MR of the brain 10 weeks after starting vismodegib.

A. FLAIR B. FLAIR C. DWI D. DWI E. T1W contrast F. T1W contrast

Axial cross-sections showing the almost complete disappearance of areas of signal alteration, with reduced alteration in diffusion and the absence of enhancement with contrast in tumor bed and lesions having a metastatic appearance (arrows).

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