Glioblastoma adaptation traced through decline of an IDH1 clonal driver and macro-evolution of a double-minute chromosome - DTU Orbit (15/03/2019)

**Glioblastoma adaptation traced through decline of an IDH1 clonal driver and macro-evolution of a double-minute chromosome**

**Background:** Glioblastoma (GBM) is the most common malignant brain cancer occurring in adults, and is associated with dismal outcome and few therapeutic options. GBM has been shown to predominantly disrupt three core pathways through somatic aberrations, rendering it ideal for precision medicine approaches.

**Methods:** We describe a 35 year-old female patient with recurrent GBM following surgical removal of the primary tumor, adjuvant treatment with temozolomide, and a 3-year disease-free period. Rapid whole genome sequencing (WGS) of three separate tumour regions at recurrence was performed and interpreted relative to WGS of two regions of the primary tumour.

**Results** We found extensive mutational and copy number heterogeneity within the primary tumour. We identified a TP53 mutation and two focal amplifications involving PDGFRA, KIT and CDK4, on chromosomes 4 and 12. A clonal IDH1 R132H mutation in the primary, a known GBM driver event, was detectable at only very low frequency in the recurrent tumour. After subclonal diversification, evidence was found for a whole genome-doubling event and a translocation between the amplified regions of PDGFRA, KIT and CDK4, encoded within a double minute chromosome also incorporating miR26a-2. The WGS analysis uncovered progressive evolution of the double minute chromosome converging on the KIT/PDGFRα/PI3K/mTOR axis, superseding the IDH1 mutation in dominance in a mutually exclusive manner at recurrence, consequently the patient was treated with imatinib. Despite rapid sequencing and cancer-genome guided therapy against amplified oncogenes, the disease progressed, and the patient died shortly after.

**Conclusions:** This case sheds light on the dynamic evolution of a GBM tumor, defining the origins of the lethal subclone, the macroevolutionary genomic events dominating the disease at recurrence and the loss of a clonal driver. Even in the era of rapid WGS analysis, cases such as this illustrate the significant hurdles for precision medicine success.

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