

IDH1-Mutant Glioblastoma with MSH6 Germline Mutation

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ARTICLE INFO

Received: 📅 February 09, 2021

Published: 📅 February 15, 2021

Citation: Martín-Soberón MC, Hernández Laín A, Rodríguez V, Cantero D, Ruano Y, et al. IDH1-Mutant Glioblastoma with MSH6 Germline Mutation. Biomed J Sci & Tech Res 33(5)-2021. BJSTR. MS.ID.005472.

ABSTRACT

Hereditary non-polyposis colorectal cancer (Lynch syndrome) is a multiorgan cancer syndrome, which is caused by an autosomal dominant mutation in germ line in the DNA mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6* and *PMS2* [1]. The diagnosis and follow-up by expert oncologists play an important role in the screening and early diagnosis of tumors in these patients. The malignancies associated to MSH6 germline mutation include colorectal, endometrial, small bowel, urinary tract, and brain tumors. However, brain tumors represent a rare and relatively uncharacterized tumor type in Lynch syndrome [2].

Keywords: Glioblastoma; *IDH-1* Mutant; Mismatch Repair (MMR); Lynch Syndrome

Introduction

We present a 36-year-old female affected of ulcerative proctitis treated with rectal mesalazine and with no other pathological previous history. Her father had been diagnosed of Lynch Syndrome with germinal mutation in *MSH6* c.3850dupA (p.Thr1284AnsfX5).

Clinical Summary

In October 2012, the patient presented partial seizures and two months later, a rapidly progressive motor dysphasia was

established. In February 2013, a cranial magnetic resonance imaging (MRI) showed a left frontotemporal contrast-enhancing lesion with associated edema. Levetiracetam 500 mg twice a day was initiated with control of the seizures and on February 28th, 2013 a macroscopic complete resection was carried out with favorable evolution after surgery. Radiological evolution is showed in (Figure 1).

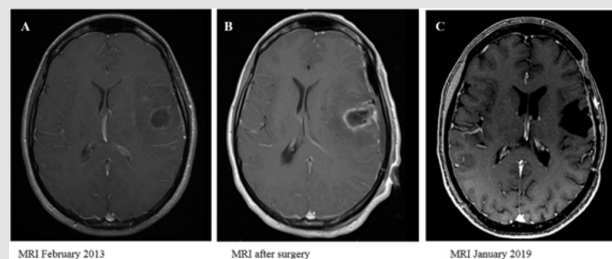


Figure 1:

- T1-weighted post-gadolinium MRI pre-surgery;
- post-surgery and
- last study after a progression-free interval of 6 years.

Pathological Findings

Most of the tumor cells were gemistocytic neoplastic astrocytes, with globose, well-defined eosinophilic cytoplasm with displacement of the nucleus to the periphery (Figure 2). The mitotic index was 2 mitosis per 10HPF. Some vessels with endothelial proliferation were observed. There were no foci of necrosis. In the immunohistochemical study, the tumor cells were positive for *IDH-1* (anti-*IDH1 R132H*), and *p53* (more than 70% of tumor cells) and they presented loss of *ATRX* nuclear expression. The MIB-1 index was 3%. Immunohistochemical analysis of *MSH6* protein showed absence of nuclear staining of tumor cells. The histologic diagnosis was Glioblastoma, WHO grade IV, *IDH1*-mutated. Next generation sequencing (NGS) panel (Foundation Medicine) was performed in DNA isolated from FFPE tumor tissue. The Foundation Medicine T7 test assay interrogates 395 genes for base substitutions, insertion-deletions and copy number changes. Histological image and NGS

results are presented in (Figure 2). Due to the anatomopathological diagnosis of *IDH-1* mutated and *ATRX* mutated glioblastoma standard treatment with Stupp protocol was initiated. Patient received chemoradiotherapy with total radiotherapy dose of 60 Grays administered in 30 sessions with concurrent daily temozolomide from April 17th to June 6th, 2013 followed by six cycles of temozolomide. Follow-up was afterwards initiated with periodic MRI without any evidence of tumor relapse. In fact, there is no evidence of disease in the last MRI performed in January 2019.

In October 2015 genetic diagnosis was performed due to family history of *MSH6* mutation and positive *MSH6* mutation in tumor sample detected with NGS (Foundation Medicine Panel). This result was confirmed with the detection of mutated *MSH6* p.Thr1284AsnfsX5 in patient's germinal line and also with the absence of *MSH6* immunohistochemical staining in the tumor cells (Figure 2).

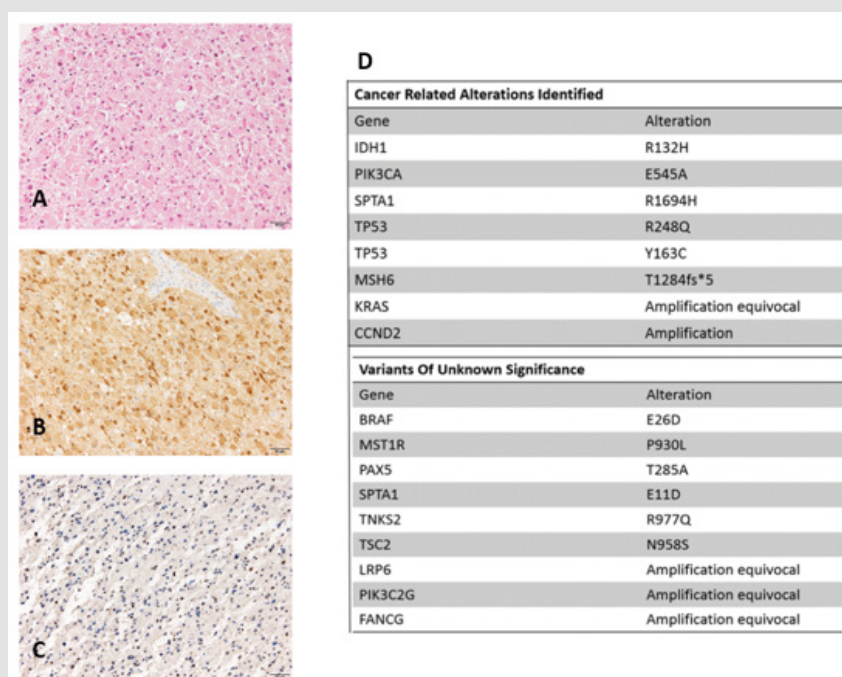


Figure 2:

- Resection tissue shows conspicuous proportion of gemistocytic neoplastic astrocytes (hematoxylin & eosin staining)
- Tumor cells are positive for mutant *IDH1* (anti-*IDH1 R132H*)
- Immunohistochemical analysis of *MSH6* shows absence of nuclear staining of tumor cells
- Foundation Medicine panel results.

Discussion

Some efforts have been made to understand tumorigenesis of different tumors in Lynch syndrome [3]. Nowadays it is not clearly understood why certain locations are more susceptible than others to develop cancer in the context of deficient MMR. Lynch syndrome. It has been estimated to confer a 1%–6% risk of brain tumors [4]. In each tumor location, it seems to occur different molecular changes after predisposing MMR deficiency. To date, association between

MSH6 mutation and glioblastoma drug resistance to temozolomide has been briefly described. Small series of cases showed that somatic inactivation of *MSH6* is reported in recurrent glioblastoma treated with alkylating agents but not in pre-treatment samples [5]. Additionally, *MSH6* mutations are associated with resistance to chemotherapy in recurrent GBM [5]. Regarding Lynch syndrome, brain tumors occurred in 14% of the families and all glioblastoma patients described so far were *IDH* wt [6]. The peculiarity of this case

consists in the favorable clinical evolution and its molecular profile with *IDH1* mutation. In fact, the patient is currently asymptomatic and disease-free after 6 years since diagnosis. We hypothesize that the phenotype associated with *IDH1* mutation prevails over the hypermutated phenotype linked to *MSH6* mutation. A matter to be discussed is if the *IDH1* mutation was a consequence of the MMR deficiency.

Acknowledgement

This work was funded by project PI 17/01621 to JMS-S, from the Instituto de Salud Carlos III (Ministry of Economy, Industry and Competitiveness) and co-funded by the European Regional Development Fund, and approved by the Ethics Committee of our Institution.

Disclosures

Authors included in this case report declare that they have no conflict of interest.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2021.33.005472

Martín-Soberón MC. Biomed J Sci & Tech Res



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Submission Link: <https://biomedres.us/submit-manuscript.php>

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