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# IDH1 mutated low grade astrocytoma occurring in MSH2 mutated Lynch syndrome family

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ABSTRACT

Lynch syndrome (LS) is an autosomal dominant tumour predisposition syndrome caused by a germline mutation in one of the DNA mismatch repair (MMR) genes.Patients with these mutations have an increased risk of brain tumours, the vast majority of which are glioblastomas and medulloblastomas, and their occurrence has been termed Turcot Syndrome. The case presented herein of a member of a Lynch syndrome family with an MSH2 mutation expands the spectrum of brain tumours occurring in Lynch syndrome to include low grade astrocytomas, and is the first reported case of an IDH1 (R132H) mutated brain tumour occurring in a Lynch syndrome family.



## 1. Introduction

Lynch syndrome (LS), previously known as hereditary nonpolyposis colorectal carcinoma, is an autosomal dominant tumour predisposition syndrome. It is caused by a germline mutation in one of the following DNA MMR genes: MLH1 (MutL homologue 1), MSH2 (MutS homologue 2), MSH6 (MutS homologue 6), or PMS2 (Postmeiotic segregation 2). Patients with a pathogenic DNA MMR gene mutation have a 10–50% risk for developing colorectal carcinoma at an early age (mean 45–50 years) and extracolonic malignancies can occur including endometrial, ovarian, hepatic, pancreatic and ureteric carcinomas and brain tumours [1,2].Although the 1–3% lifetime risk of brain tumours is low compared to other extracolonic tumours in LS families [1], this risk is 6 fold that of the general population and its occurrence has been termed Turcot Syndrome. The brain tumours previously described in Lynch/Turcot syndrome have mostly been high grade gliomas, predominantly glioblastomas, and less commonly, medulloblastomas [1,3–6].A recent European study described the risk of developing brain tumours being highest (2.5%) in Lynch syndrome patients with MSH2 mutations, contained the first description of low grade astrocytoma in Lynch syndrome (1/47 gliomas was a pilocytic astrocytoma (WHO grade I), and 1/47 was a diffuse astrocytoma (WHO grade II)), and showed universal negativity for mIDH1 immunoreactivity in Lynch syndrome associated glioma [7].The present case adds to the sparse literature on low grade astrocytomas in Lynch syndrome and is the first report of a Lynch syndrome associated IDH1 R132H mutated glioma.

The reader is reminded of previous work on expression of MLH1, MSH2 and MSH6 immunohistochemistry in gliomas; namely that 43% of astrocytoma have reduced expression of at least one MMR protein, MSH2 negative staining is more frequent in lowgrade astrocytomas (45%) than in high-grade astrocytomas (16%) [8], as well as the recent interest in MMR deficiency as a predictor of temozolamide response, recurrence and as a consequence of temozolamide treatment [9,10].

## 2. Case and methods

A 72 year old man had a previous diagnosis of colorectal carcinoma and a family history of LS that included: colorectal carcinomas in his father, brother, niece and several paternal aunts and uncles, breast carcinoma and multiple sebaceous adenomas in his sister and ureteric carcinoma and melanoma in his brother. Some family members met criteria for the Muir–Torre variant of LS but our patient did not and no previous family members had a brain tumour/Turcot syndrome. An MSH2 mutation was found in the patient, his niece and sister (560 T $_amp_$gt; C, exon 3). Our patient presented with rapidly progressive memory impairment and magnetic resonance imaging demonstrated a 3 cm irregularly enhancing tumour of the third ventricle, involving bilateral thalami and superior midbrain with obstructive hydrocephalus and leptomeningeal enhancement. The tumour was mostly resected but the patient died 1 month later. Pathologic workup was performed on the surgically resected brain tumour tissue; H$_amp_$amp;E and immunohistochemistry for GFAP, p53, Ki67 and mIDH1 (R132H). Nuclear expressions of MLH1, MSH2, MSH6 and PMS2 within the

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**Table 1**

| Immunohistochemical antibody | Manufacturer and dilution |
|---|---|
| GFAP | Cellmark, prediluted |
| p53 | Ventana, prediluted |
| Ki67 | Ventana, prediluted |
| mIDH1 (R132H) | Histobio Tec, 1/50 |
| MLH1 | Biocare, 1/25 |
| MSH2 | Calbiochem 1/1000 |
| MSH6 | BD, 1/400 |
| PMS2 | BD, 1/100 |

tumour were compared to the endothelial and ependymal cells within the brain. Immunohistochemical antibodies used are listed in Table 1. No post mortem examination was done.

## 3. Results

H$_amp_$amp;E stained sections showed a low grade astrocytoma with intraparenchymal, leptomeningeal and intraventricular components (Fig. 1a). The intraparenchymal component was an infiltrative low grade astrocytoma with oval nuclei and a densely fibrillary

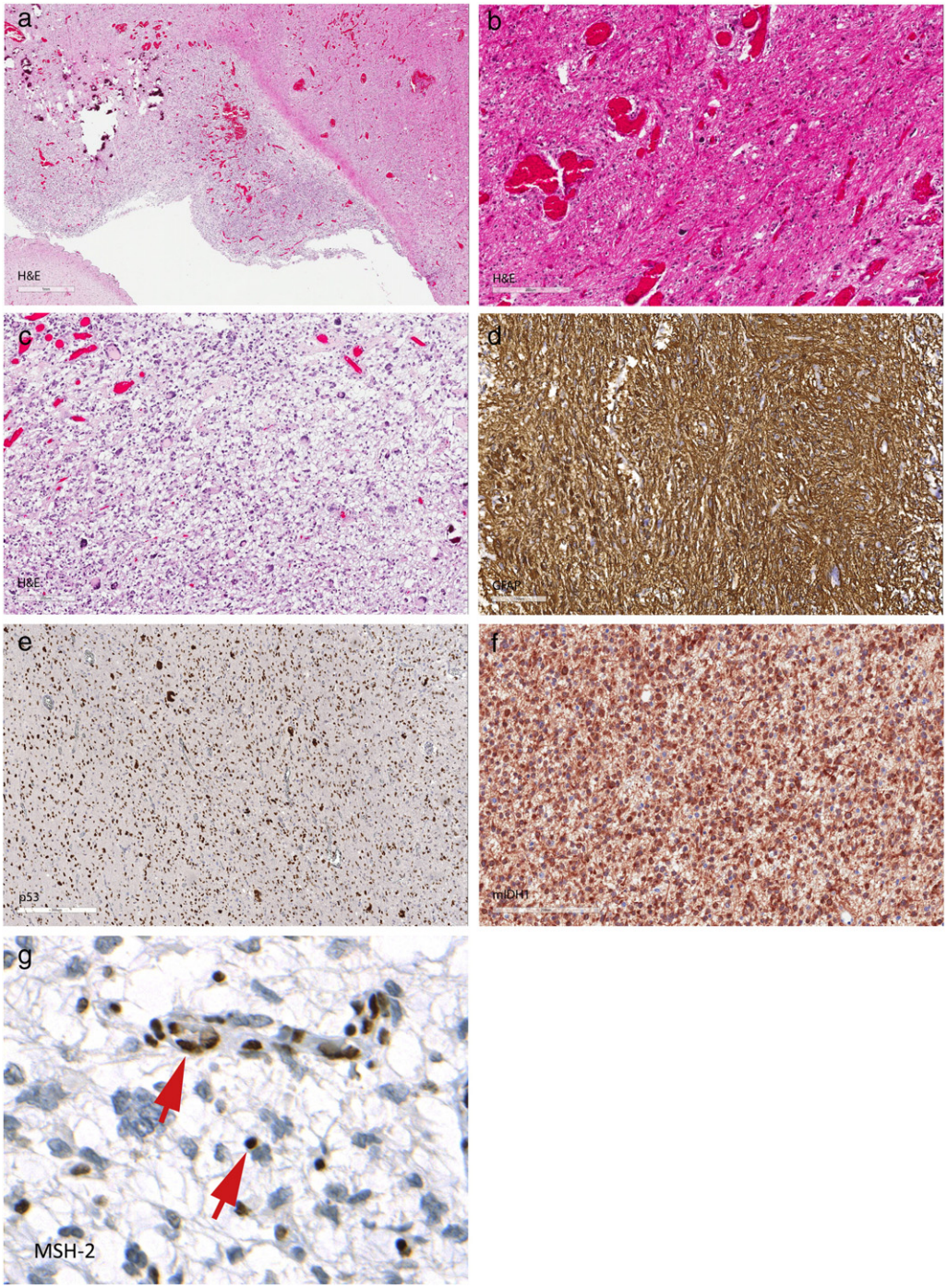


**Fig. 1.** Low grade astrocytoma a — Low power H$_amp_$amp;E showing the tumour to have intraparenchymal and intraventricular components; b — H$_amp_$amp;E of the intraparenchymal component showing an infiltrative low grade astrocytoma with oval nuclei and a densely fibrillary background; c — the intraventricular component is more discohesive and cellular with rounder more eccentric nuclei and scattered multinucleated giant cells; the tumour cells are strongly positive for GFAP (d), p53 (e), and mIDH1 (R132H) (f), and there is loss of nuclear MSH2 staining compared to the normally stained endothelia and lymphocytes (red arrow on (e)).

background (Fig. 1b) and eosinophilic granular bodies and calcifications were seen focally. The intraventricular and leptomeningeal components were discohesive and myxoid with more pleomorphic eccentric nuclei and scattered multinucleated cells (Fig. 1c). Mitoses, necrosis and microvascular proliferation were not seen. On immunohistochemical staining most tumour cells were strongly immunopositive for GFAP which highlighted examples of coarse cytoplasmic processes and bipolar lesional cells (Fig. 1d), and they were strongly positive for p53 (Fig. 1e) and mIDH1 (R132H) (Fig. 1f). Nuclear ATRX expression was lost. The Ki67 proliferative index was less than 1% throughout. The tumour cells showed retention of nuclear MLH1 and PMS2 staining and complete loss of MSH2 and MSH6 compared to the normally stained ependyma and endothelia (Fig. 1g).

## 4. Discussion

There are two unique aspects to our case.First, low grade astrocytoma histology has only rarely been previously reported in LS families [6,7].Second, to our knowledge, this is the first case of IDH1 mutated glioma reported in the setting of an LS family [8,9].Whether the presence of a mutated IDH1 glioma in a patient with MSH2 mutation is a chance occurrence or is informative about oncogenesis remains uncertain.

## 5. Conclusion

Brain tumours reported in Lynch syndrome families have predominantly been glioblastoma or medulloblastoma, and the present case expands this spectrum to include mIDH1 (R132H) mutated low grade astrocytoma.

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