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Corticotroph pituitary carcinoma in a patient with Lynch syndrome (LS) and pituitary tumors in a nationwide LS cohort

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Short title: Pituitary carcinoma in Lynch syndrome.

Key words: pituitary carcinoma, DNA mismatch repair proteins, Lynch syndrome

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Abstract

Context: Lynch syndrome is a cancer predisposing syndrome caused by germline mutations in genes involved in DNA mismatch repair (MMR). Patients are at high risk for several types of cancer, but pituitary tumors have not previously been reported.

Case: A 51-year old man with LS (*MSH2* mutation) and a history of colon carcinoma presented with severe Cushing's disease and a locally aggressive pituitary tumor. The tumor harbored a mutation consistent with the patient's germline mutation, and displayed defect MMR function. Sixteen months later, the tumor had developed into a carcinoma with widespread liver metastases. The patient prompted us to perform a nationwide study in LS.

Nationwide study: A diagnosis consistent with a pituitary tumor was sought for in the Swedish National Patient Registry. In 910 patients with LS, representing all known cases in Sweden, another two clinically relevant pituitary tumors were found; an invasive non-secreting macroadenoma, and a microprolactinoma, i.e. in total three tumors vs. one expected.

Conclusion: Germline mutations in MMR genes may contribute to the development and/or the clinical course of pituitary tumors. Since tumors with MMR mutations are susceptible to

treatment with immune checkpoint inhibitors we suggest to actively ask for a family history of LS in the work up of patients with aggressive pituitary tumors.

Introduction

Lynch syndrome (LS), is an autosomal dominant cancer predisposing syndrome caused by germline mutations in one of the DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) or within the epithelial adhesion molecule (*EPCAM*) gene adjacent to the *MSH2* gene (1). An additional somatic event in the wildtype allele is necessary to inactivate both MMR gene copies. Defective MMR proteins result in an inability to repair mismatched bases in DNA sequences. The tumors show microsatellite instability (MSI) which reflects an increased rate of mutations, primarily insertions/deletions in short DNA repeats (2). The syndrome has a high penetrance with 70-90 % lifetime risk for cancer in mutation carriers (3), for details see Prospective Lynch Syndrome Database by InSiGHT, <http://lscrisk.org/>. Colorectal cancer is the most common tumor type, followed by endometrial cancer in women. Patients with LS are at risk for a wide spectrum of other tumors including ovarian, urinary tract, small bowel, gastric, hepatobiliary, and malignant brain tumors. Recently, a neuroendocrine tumor, adrenal carcinoma, was reported to be part of the syndrome (4). The occurrence of pituitary tumors in LS has not been previously addressed.

Case

A 51-year old man presented with Cushing's syndrome, marked hypokalemia (1.9-2.2 mmol/L), UFC 53 times above the ULN, p-ACTH 68-72 (ref. <10 pmol/L). The patient belonged to a family with Lynch syndrome and had a mutation in *MSH2*, c.1587delA (p.Glu530Lysfs). One of his first-degree relatives had a colon carcinoma. The patient had been operated for a colon carcinoma at the age of 39. MRI showed a pituitary tumor eroding the floor of the sella and extending into the sphenoidal sinus (Figure 1a). Pituitary surgery

was performed. The tumor tissue was positive for ACTH, had high mitotic numbers, atypical nuclei, Ki-67 40%, p53 positive in the majority of cells. ¹⁸F-FDG-PET/CT scan of the thorax and abdomen did not show any metastases. After surgery, ACTH transiently decreased to 11 pmol/L and s-cortisol to 42 nmol/L. Subsequently, the patient had another pituitary surgery, fractionated radiotherapy 50 Gy, and bilateral adrenalectomy (BA) because of hypercortisolism not controlled by ketoconazole and metyrapone. After the BA, ACTH remained below 100 pmol/l for 10 months, then rapidly increased to 43000 pmol/L with liver enzymes elevated. CT scan showed multiple liver metastases (Figure 1b) and a biopsy confirmed a pituitary origin. After five cycles of temozolomide CT showed $\geq 50\%$ regression of the liver metastases, p-ACTH gradually decreased to nadir 5075 pmol/L. After 6 months on temozolomide there was a progression of the liver metastases and spread to the skeleton. Addition of capecitabine did not arrest the course. The patient died two years after diagnosis of the pituitary tumor.

Analyses of MMR and MSI were performed on paraffin-embedded tumor removed at the first surgery, for methods see Joost et al (5). The protein expression of MLH1, MSH2, MSH6 and PMS2 in neoplastic cells was classified as retained (presence of nuclear staining), lost, or reduced. Instability for 1 of 5 markers was classified as MSI-low, instability for ≥ 2 as MSI-high, and stability for all markers as microsatellite stable. The tumor of the patient showed unambiguous loss of MSH2 and MSH6 (Figure 2) with retention of MLH1 and PMS2 consistent with the patient's germline mutation, and was MSI-low.

Nationwide study

The study population was recruited from LS registries in Sweden, started between 1990 and 2002 (University Hospitals Lund/Malmö, Linköping, Gothenburg, Stockholm, Uppsala,

Umeå), which include all families with a confirmed germline MMR mutation. With use of the unique personal identification number in Sweden, linkage between the LS cohort and the Swedish National Patient Registry was performed. The Patient Registry collects information about diagnoses on every hospital admission or polyclinic visit in Sweden. Patients with LS and WHO ICD-9 codes (1987 to 1996) and ICD-10 (1997 to Dec 2015) consistent with pituitary tumors and sequels of their treatment; hypopituitarism, diabetes insipidus, and pituitary disease not further specified were identified. In every case with a pituitary diagnosis, the relevant medical records and imaging results were reviewed.

Ethics

The study was approved by the Ethics Committee of Lund University, Sweden, Dnr 2015/365.

Pituitary disease in the nationwide LS cohort

In total 910 (M 426/F 484) unique individuals with an LS-associated mutation were found (*MLH1* 39.1%; *MLH1/MSH2* 0.1%; *MLH1/PMS2* 0.7%; *MSH2* 29.8%; *MSH2/MSH6* 0.2%; *MSH6* 22.1%; *PMS2* 7.5%; *EPCAM* 0.1%, and *EPCAM/MSH2* 0.4%). Age at end of study (December 2015) or age at death ranged from 19-96, median 54 years. 114 persons were diseased, median age 69, range 21-92 years.

The study identified five cases with pituitary disease. Two did not have a pituitary tumor; one had panhypopituitarism after surgery for an anaplastic astrocytoma, one was diagnosed with GH deficiency during childhood and developed complete hypopituitarism in adolescence. Imaging showed empty sella.

Three of LS patients had a clinically significant pituitary tumor (Table 1). Case 1, see above. Case 2, a female with *MSH6* germline mutation (c.2062_2063delGT), had a microprolactinoma diagnosed at the age of 39 during investigation of infertility and galactorrhea. She was treated with dopamine agonists, prolactin normalized and the tumor partially regressed. At the age of 49 she was diagnosed with an endometrial carcinoma. Other tumors among her first degree relatives included prostate cancer and a colon polyp. Case 3, a male with a *PMS2* mutation (c.2113C>A) developed visual disturbances at the age of 44 due to an invasive, non-secreting macroadenoma. The tumor had a solid component in the right side 20x17x18 mm, and a cystic part 20x5x15 mm in the left side (Figure 1c). At transsphenoidal surgery, tumor tissue was by mistake not sent for histopathology. At the age of 52 he was diagnosed with a colon carcinoma. One of his first degree relatives had a colon carcinoma.

Discussion

This case is the first description of a pituitary tumor in a patient with LS. In addition to the patient's inherited *MSH2* mutation, the tumor displayed MSI, a typical feature of MMR deficiency resulting from functional inactivation of both *MSH2*-alleles. At diagnosis, there were no detectable metastases, 16 months later there was a widespread dissemination to the liver. Considering that the average lag time from diagnosis to metastases is 6.6 years in pituitary carcinomas (6), this course was rapid.

The combination of Lynch syndrome and an aggressive pituitary tumor made us investigate the occurrence of pituitary tumors in a national cohort of LS. Among 910 LS patients two additional pituitary tumors were found; another large invasive adenoma, and a microprolactinoma diagnosed in the work-up of infertility and galactorrhea. The reported

prevalence of pituitary tumors in the general population is approximately 1:1000; 0.94:1000 in Belgium (7), and 1.15:1000 in Iceland (8). Thus, three clinically significant pituitary tumors in the LS cohort of 910 subjects is more than expected. About five percent of pituitary tumors occur in a familial setting including FIPA (*AIP*), MEN1 (*MEN1*), MEN4 (*CDKN1B*), Carney Complex (*PRKARIA*), *DICER1*, and *SDHx* mutations (9). Hereditary tumors seem to occur at an earlier age and be more aggressive than sporadic pituitary tumors (9).

MSI, the phenotypic consequence of MMR deficiency, seems rare in benign pituitary adenomas, and was reported in none of 100 (10), and in one of 31 adenomas (11), respectively. In apparently sporadic aggressive pituitary tumors and carcinomas MSH6 deficiency was reported in 4 of 13 patients; expression of other MMR proteins was not assessed (12). Intact MMRs were found in two others studies on a total of 23 patients with sporadic aggressive pituitary tumors (13,14). Notably, loss of MSH6 was observed during transformation of an atypical prolactinoma into a pituitary carcinoma (15). This supports that MMR gene mutations could contribute to the development of aggressive pituitary tumors.

MMR-deficient tumors express an abundance of mutated proteins and harbor infiltrating cytotoxic T-cells (16). In this context, MMR-deficient tumors of various types were recently shown to be susceptible to treatment with a programmed death (PD1) pathway blocking antibody. An objective response was seen in 4/10 patients with progressive metastatic disease upon treatment with pembrolizumab vs. in none of 18 patients with intact MMRs (17).

Conclusion

The present findings indicate that mutations in MMR genes could predispose to the development of pituitary tumors. Of particular interest was that two of the three identified patients had invasive large tumors of which one rapidly evolved into a carcinoma. Notably, in

two of the affected patients the pituitary tumor was the first manifestation of LS. Endocrinologists should be aware of the possibility of MMR deficiency in aggressive pituitary tumors, especially since these tumors may benefit from treatment with PD1 blockade. Our findings also suggest that surveillance for pituitary tumors should be considered in LS mutation carriers. Further, in the work-up of patients with aggressive pituitary tumors, we propose that a family history of solid tumors typical for LS, especially colon and endometrial cancer, should be asked for.

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Table 1. Patients with pituitary tumors in the Swedish LS Cohort (n=910)

Age*/ Sex	Germline mutation	Pituitary MMR (IHC)	Pituitary MSI	Pituitary tumor	Age at diagnosis	Pituitary treatment	Clinical presentation and course	Other tumors
53/M	<i>MSH2</i>	loss of MSH2 and MSH6	low (1 of 5 markers)	corticotroph carcinoma, liver and skeletal metastases	51	surgery*3, radiation, bilateral adrenalectomy, temozolomide, capecitabine	Severe Cushing's disease. Progression, died two yrs after diagnosis	colon ca 39 yrs old
60/F	<i>MSH6</i>	NA	NA	microprolactinoma	39	dopamine agonist (DA)	Infertility, galactorrhea. PRL normalized on DA, no shrinkage of tumor	endometrial ca 49 yrs old
59/M	<i>PMS2</i>	NA	NA	invasive nonfunctioning macroadenoma	48	transsphenoidal surgery	Vision defect. Normalized after surgery, no hormonal deficits.	colon ca 52 yrs old

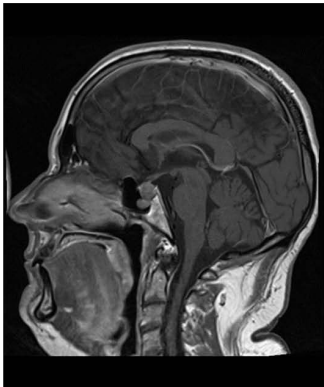
*age at end of study or at death; MMR DNA mismatch repair proteins; IHC immunohistochemistry; MSI microsatellite instability; NA not available.

Figure legends

Figure 1. (a) Case 1, MRI of the corticotroph pituitary tumor at diagnosis. (b) CT scan of the liver showing widespread metastases from the pituitary carcinoma. (c) Case 3, MRI of an invasive, clinically silent macroadenoma with a solid and a cystic component.

Figure 2. Case 1, Immunohistochemistry of MMR proteins in the pituitary tumor.

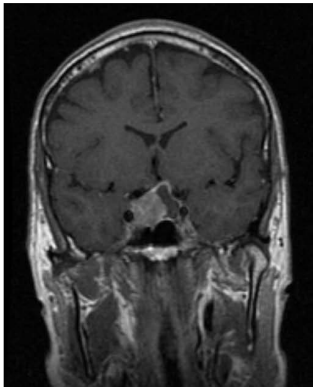
Magnification x 20. Upper row, loss of MSH2 and MSH6, lower row, retained staining of MLH1 and PMS2. MMR proteins form functional heterodimers (MLH1/ PMS2, and MSH2/MSH6) with MLH1 and MSH2 being the two obligatory proteins for the stability of their respective heterodimer. Mutations in MSH2 lead to loss of expression of both MSH2 and MSH6, while mutations in MSH6 lead to loss of expression of MSH6 only.



(a)

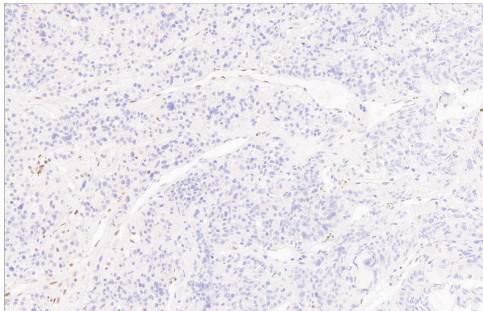


(b)

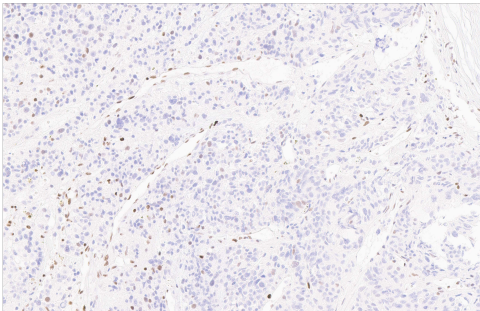


(c)

MSH2 negative



MSH6 negative



MLH1 positive



PMS2 positive

