

Case Report:

A rare case of Turcot syndrome

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ABSTRACT

Turcot's syndrome is a rare genetic disorder clinically characterised by concomitant occurrence of primary brain tumour and colorectal polyposis. It is commonly seen in association with two other syndromes, namely, hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP). It is characterized by an increased risk for early onset of other tumours including of endometrium, stomach, small intestine, hepatobiliary system, kidney, ureter, brain and ovary. We report the rare occurrence of Turcot syndrome in a 13-year-old girl who presented with focal seizure.

Key words: *Adenomatous Polyposis Coli gene, familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, mismatch repair gene, Turcot syndrome*

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INTRODUCTION

Turcot's syndrome is a genetic disorder clinically characterized by concomitant occurrence of primary brain tumour and colorectal polyposis. It is a rare syndrome and commonly occurs in association with two other more common syndromes (i) hereditary nonpolyposis colorectal cancer (HNPCC) (Lynch syndrome, Type I Turcot syndrome); and (ii) familial adenomatous polyposis (Type II Turcot syndrome). The former is associated with germ line mutations in deoxyribonucleic acid (DNA) mismatch repair (MMR) genes and the later with germ line mutations in adenomatous polyposis coli (APC) gene.^{1,2} The DNA MMR genes include Mut L homolog1 (MLH1), Mut S homolog2 (MSH2), Mut S homolog 6 (MSH 6), Post meiotic segregation increased 2 (PMS2) and several others. When Turcot syndrome occurs in association with familial adenomatous polyposis (FAP) the primary brain tumour is usually a medulloblastoma and when it occurs in association with Lynch syndrome the primary

brain tumour is a astrocytoma or glioblastoma multiforme. The clinical criteria used to identify HNPCC include Amsterdam criteria II³ and revised Bethesda guidelines.⁴

As per the Amsterdam II criteria³ the following are required to diagnose HNPCC. There should be at least three relatives with colorectal cancer or with a Lynch Syndrome associated cancer, namely, cancer of the endometrium, small bowel, ureter or renal pelvis. One relative should be a first-degree relative of the other two; at least two successive generations should be affected; at least one tumour should be diagnosed before the age of 50 years; FAP should be excluded in the CRC case if any; and tumours should be verified by histopathological examination, identify HNPCC.

As per the revised Bethesda guidelines,⁴ the following are required to identify HNPCC colorectal cancer diagnosis in a patient under 50 years of age, presence of synchronous, metachronous colorectal or other Lynch Syndrome-related tumours regardless of age, colorectal cancer with Mut S homologue

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(MSH)-phenotype diagnosed in a patient aged under 60 years; patient with colorectal cancer and a first-degree relative with a Lynch Syndrome-related tumour, with one of the cancers diagnosed at the age under 50 years; patients with CRC with two or more first-degree or second-degree relatives with a Lynch syndrome-related tumour, regardless of age.

Demonstration of the absence of mutated MMR gene proteins in tumour tissue by immunohistochemistry will help screening the patients, when clinical criteria suggest Turcot's syndrome. The diagnosis of Turcot's syndrome can be confirmed by demonstrating the specific germ line mutations in a clinically suspected case by molecular genetic testing.⁵⁻⁷

CASE REPORT

A 13-year-old girl was admitted to our hospital in 2007 with a history of focal seizures with secondary generalization. Postictally patient had weakness in left upper and lower limbs with deviation of mouth to right side. On examination patient was conscious, oriented, bilateral pupils were reacting to light and left upper motor neuron facial paresis was present. Power was 4/5 in left upper and lower limbs. Fundoscopy was normal and there was no papilloedema. Magnetic resonance imaging (MRI) brain revealed a heterodense lesion with heterogeneous enhancement post-contrast with features of intra-lesional bleed, perilesional oedema and mass effect involving the body of corpus callosum in the right frontoparietal region (Figure 1).

She underwent right frontoparietal craniotomy and decompression of the tumour. Intraoperatively tumour was greyish, soft and moderately vascular. Histopathological examination revealed an anaplastic oligodendroglioma/glioblastoma with focal oligodendroglial components (Figure 2). Immediate post-operative computed tomography (CT) of the brain revealed tumour decompression with speckles of

pneumocephalus with minimal operation site collection. Patient received adjuvant radiotherapy (5600 cGy/28 fractions) during October–November 2007 followed by lomustine (CCNU) therapy from January to July 2008. Follow up CT of brain in September

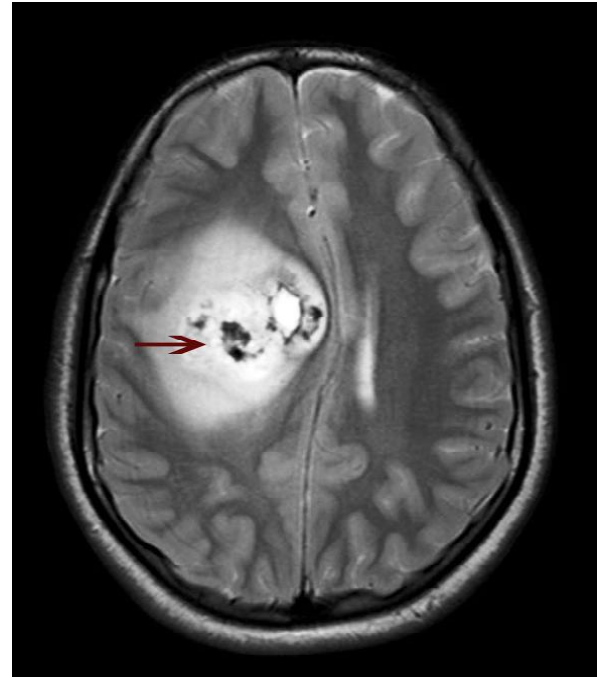


Figure 1: Axial T2-weighted contrast enhanced MRI of the brain showing a tumour in the fronto parietal region (arrow)

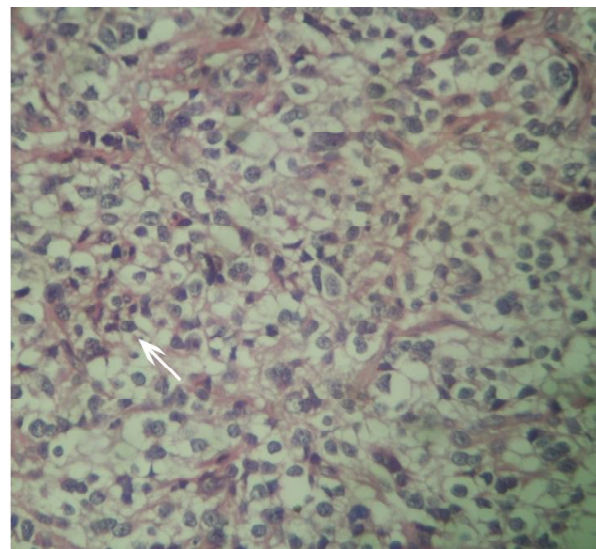


Figure 2: Photomicrograph showing sheets of oligodendrocytes with round to oval polyhedral tumour cells having clear cytoplasm exhibiting moderate pleomorphic vesicular nuclei and prominent nucleoli suggestive of oligodendroglioma glioblastoma with focal oligodendroglial components (arrow) (Haematoxylin and eosin, $\times 400$)

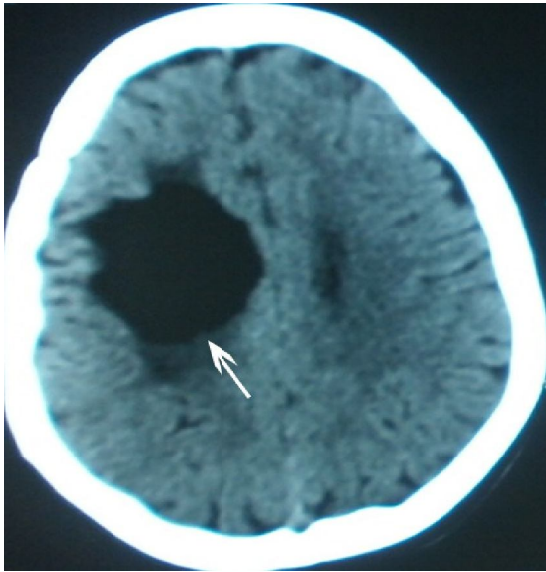


Figure 3: CT brain of the patient 6 years after surgery showing non-recurrence of tumour

2013 showed no recurrence of tumour (Figure 3). She was asymptomatic for a period of 6 years. None of the family members of the patient were found to have colorectal or any other turcot associated tumors after thorough investigation.

The same girl was admitted again in 2013 with complaints of loss of appetite, colicky lower abdominal pain and bleeding per rectum. On clinical examination patient was thinly built. Moderate pallor was evident. Her heart rate was 96/min and blood pressure 100/70 mm Hg. There was a palpable mass in the left side of the abdomen. Haemoglobin was 7.4g/dL; liver and renal functions were normal. Echocardiography did not reveal any cardiac abnormality. Abdominal ultrasonography revealed focal bowel wall thickening in the descending colon and there was single horse shoe shaped kidney. Uterine endometrial thickness was normal and endometrial cancer was ruled out. CT abdomen revealed circumferential wall thickness of proximal descending colon with luminal narrowing, pericolic lymph nodes and multiple polypoidal lesions in rectum and colon. Colonoscopy revealed few colonic polyps with an ulceronodular growth in descending colon.

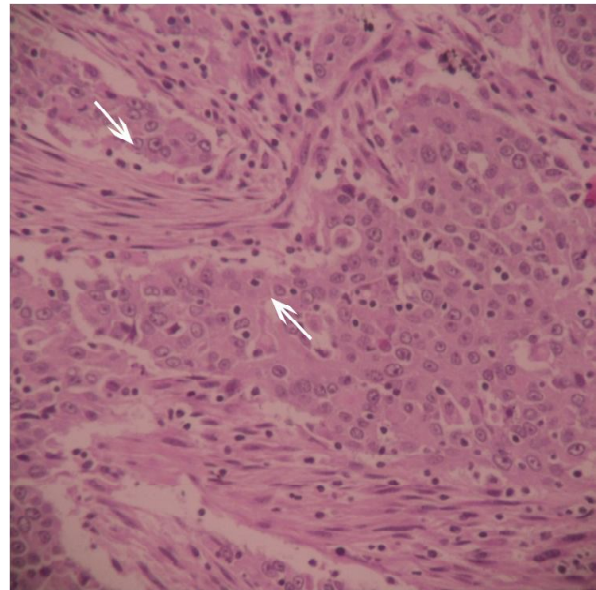


Figure 4: Photomicrograph of colonic tumor showing cells arranged mostly in sheets, cords, trabeculae and invading into muscularis propria (arrows) suggestive of adenocarcinoma (Haematoxylin and eosin, $\times 400$)

Upper gastrointestinal (GI) endoscopy was normal. Histopathological examination of the polyps revealed tubulovillous adenoma with high grade dysplasia. There were palpable masses in both the breasts and on fine needle aspiration cytology (FNAC) the masses were found to be fibroadenomas. Patient underwent total colectomy with end-ileostomy. Histopathological examination of the colonic growth revealed poorly differentiated infiltrating adenocarcinoma Grade III B (Figure 4). Immunohistochemistry revealed absence of MLH1 and MSH6 gene proteins with focal expression of MSH2. Patient is presently on adjuvant chemotherapy with modified oxaliptan, 5-fluoro uracil and lencovoin (FOLFOX-6) regimen.⁸

DISCUSSION

Colorectal cancer incidence rates in India are 4.3 and 3.4/100,000 men and women respectively.⁹ HNPCC is the most common hereditary colorectal cancer and accounts for 1%-6% of colorectal cancers.⁹ Only 1%-3% of the HNPCC patients develop primary brain tumours to be designated as Turcot's syndrome.

Jacques Turcot, a Canadian surgeon was the first person to describe this syndrome in the year 1959 and hence the eponym Turcot's syndrome.¹⁰ HNPCC is inherited as an autosomal dominant fashion and is characterized by an increased risk for early onset of other tumours including endometrial, stomach, small intestine, hepatobiliary system, kidney, ureter, brain and ovary.^{3,11}

The term Turcot's syndrome refers to two distinct genetic syndromes which show phenotypic variations. Large number of adenomatous polyps are common in FAP associated Turcot's syndrome where as the number of polyps in HNPCC associated Turcot's syndrome are relatively less in number. However, attenuated forms of FAP with small number of adenomas have been reported. In a series of 14 families a large number of adenomas were found in two HNPCC associated Turcot's syndrome families.¹⁰ So the two variants of Turcot's syndrome can only be distinguished by demonstrating germ line mutations in APC and DNA MMR genes. Patients with Turcot's syndrome who have small number of adenomas and onset of colorectal and primary brain tumours in childhood or adolescence are more likely to be HNPCC subtype.

Genetic characterization has important therapeutic implications. Symptoms and signs suggestive of central nervous system tumour require prompt investigation in both types of Turcot's syndrome. At risk family members of the FAP associated Turcot's syndrome who develop central nervous system tumours require genetic testing for APC gene mutations, colonoscopy surveillance for adenomas and colectomy if they develop adenomas. Family members of the HNPCC associated Turcot's syndrome should seek genetic counselling regarding genetic testing and colonoscopy surveillance is recommended for those at risk.^{10,12}

Mutations in mismatch repair genes result in a failure to repair errors in repetitive sequences that occur during DNA replication and this failure is responsible for micro satellite instability that is seen in cases of HNPCC. Absence of mutated MMR gene proteins in the tumour tissue can be demonstrated using immunohistochemistry which has a high sensitivity and specificity for screening for HNPCC. It can point directly to the mutated gene, which reduces the cost for the subsequent mutation analyses. Immunohistochemistry can also be used to demonstrate inherited cancer in deceased family members.^{3,5,6}

Molecular genetic testing could not be done in the present case. Early development of primary brain tumour and colonic cancer in early teens with small number of adenomas on colonoscopy and absence of two MMR gene proteins MLH1 and MSH6 is highly suggestive of Turcot's Syndrome as per the revised Bethesda criteria 1 and 2.¹³ Partial expression of MLH2 product in the absence of MSH6 and presence of single horse-shoe kidney are the rare manifestations in this patient. It has been reported that early onset colorectal cancer represents a biologically distinct disease, with clinico-pathologic and molecular differences compared with patients with older onset of disease. This cohort depicts a distinct molecular profile of MMR deficiency characterized by a high frequency of germ line mutations in MSH6. There is decreased frequency of frame shift mutations and increased levels of point mutations associated with MSH6 deficiency, compared with MLH1 or MSH2 deficiency.¹⁴

Colorectal cancer can be cured by early diagnosis and treatment. Identifying individuals at risk is a challenge for the clinicians. The criteria used to recognize inherited colorectal cancer were previously limited to family history alone. Now with the advent of genetic screening

tests like Immunohistochemistry the diagnostic yield can be improved to a high degree of sensitivity and specificity. Screening options may change over time as new technologies are developed and more is understood about the genetics of cancer.^{3, 15,16}

Identification of individuals at hereditary risk for cancer is an important aspect in oncology practice. Careful evaluation of the family history will provide an opportunity for the prevention and early diagnosis of hereditary colorectal cancer. Genetic counsellors can provide information about the pattern of inheritance and guidance about genetic testing. Colonic and extra-colonic surveillance can be recommended for “at risk” family members.

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