Adenocarcinoma of the Rectum in a 27-year-old Patient with Usher Syndrome : Is there a Genetic Correlation?

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To the Editor,

Usher syndrome is an autosomal recessive disorder characterized by sensorineural hearing loss and impaired vision. Patients with Usher syndrome type 1C have a germline mutation in AIE-75/harmonin. This AIE-75/harmonin binds to MCC2, homologue to MCC (mutated in colon cancer; MCC1) and is a possible tumor suppressor. Expression of AIE-75/harmonin suppresses growth of human colorectal adenocarcinoma SW480 cells.

We report a case of a young woman with Usher syndrome and a colorectal adeno-carcinoma.

A 27-year-old dark skinned woman with Usher syndrome presented at the emergency department with acute excessive fresh red rectal blood loss mixed with older brownish blood. She felt dizzy and sweaty, with tendency to lose consciousness.

In the recent past, she suffered from abdominal pain, hot flushes (sometimes fever), excessive sweating at night and diarrhea (sometimes with blood loss) often accompanied with joint pain. There is no history of weight loss. There are no urologic or gynecological abnormality's. Menstruation is regular due to oral contraception. She has no cardiothoracic complains. Because of Usher syndrome she is deaf and has an impaired sight. Two years ago the general practitioner diagnosed her with anemia.

At arrival at the emergency department the patient is hemodynamically stable. Blood pressure is 117/69 mm/Hg with a heart rate of 114 bpm. She has no fever. There are no signs of dehydration. Because of her dark skin checking for anemia is more difficult but the conjunctivae have a normal color. When we examine the patient there are no abnormalities in cardiopulmonary auscultation. Abdomen is not tender and there is a very active peristalsis. No masses are palpable. Rectal examination shows no wounds, fissures or hemorrhoids. Digital rectal examination revealed a small quantity of black colored stool.

Blood results show a decreased hemoglobin of 9.3g/dl (reference range 11.0-14.4g/dl), raised white blood cell count of 14.0x1000/mm^3 (reference range 3,5-9,8x1000/mm^3) combined with neutrophilia. CRP is 15,3mg/L (reference range 0,0-10,0mg/L). Normal kidney and liver function, no aberrant coagulation and a normal count of thrombocytes. An ultrasound of the abdomen shows no free intra-abdominal fluid and no masses.

The patient was admitted to the hospital for further investigation the day after. However during the night, there is massive rectal blood loss with hypotension and tachycardia. Urgent gastroscopy was performed but didn't show any cause of bleeding. Because the colon was impacted with blood and stool, a colonoscopy could not be performed. Though deterioration continued quickly and the patient became hemodynamically instable. Since at that time no radiologist was present a CT angiography nor angiography could be performed immediately and because of further deterioration the patient was rushed to the operating room for an explorative laparotomy.

Peroperatively a massive tumor in the rectum was found. To control the bleeding the Art mesenterica inferior was clamped and ligated first, then an ultra-low anterior resection type Hartmann was performed and a terminal colostoma was created because of the hemodynamic instability. A distal stump of 3 to 4cm could be preserved. The tumor could be resected in totally. No suspicious lymph nodes were seen.

Histopathological diagnosis showed a low grade moderately to well differentiated adeno-carcinoma of the rectum with ulcerations and extramural vascular invasion (pT3dN1M0).

Seven weeks postoperative, chemo-radiotherapy (Folfox schedule with con-comitant 5-FU during radiation) was given during 5 weeks. There were no immediate postoperative complications.

Usher syndrome (USH) is the most prevalent cause of hereditary deafness-blindness in humans and is clinically and genetically heterogeneous. It is inherited as an autosomal recessive trait and subdivided into three clinical USH types, namely USH1, USH2 and USH3 (1). Dysfunction or absence of any of the molecules related to USH disease may lead to disruption of the USH protein network causing sensorineuronal degeneration in the inner ear and the retina, inducing deafness with vestibular

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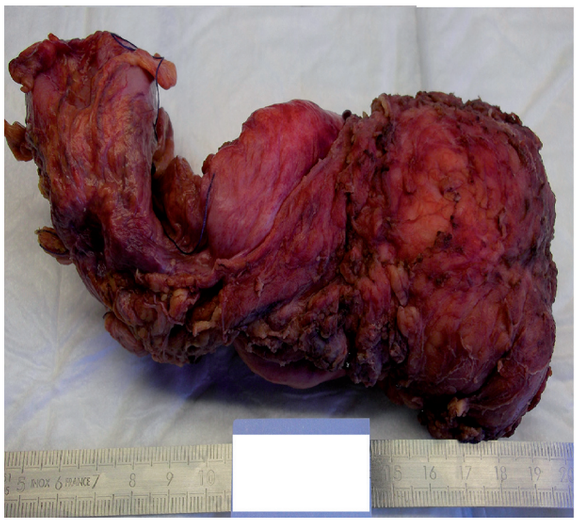

Fig. 1. — Resection specimen of the colorectal adenocarcinoma.

Fig. 2. — Macroscopic transvers section of the tumor.

dysfunction and retinitis pigmentosa respectively (2). Mutations in USH type 1 genes cause the most severe form of USH.

At least seven USH1 loci, USH1A-G, have been mapped to different chromosome regions. Mutations in AIE-75/harmonin have been shown to be the cause of Usher syndrome type 1C (1).

Now AIE-75/harmonin is also known as a colon cancer-related auto-antigen (6). It is physiologically expressed in epithelial cells with microvilli such as those of small intestine, colon, kidney, pancreas, and inner ear. AIE-75/harmonin has a role as an anchor protein and interacts with different target proteins, like tumor suppressor proteins (4,5). In colon cancer cells, loss of AIE-75/harmonin expression is a rather rare phenomenon (4,5).

S. Ishwikawa et al. searched for proteins that bind to AIE-75/harmonin. They showed a novel protein (MCC2), which is homologue to MCC (mutated in colon cancer; MCC1) tumor suppressor. MCC2 expression is absent or very low in tumor cell lines in contrast to the positive expression in the respective normal tissues, suggesting that MCC2 is also a possible tumor suppressor. However MCC1 and MCC2 have distinct binding partners and differential expression patterns in various organs, suggesting that MCC1 and MCC2 have distinct functions in the different tissues (5).

A. Hirai et al. transfected the AIE-75/harmonin gene into human colon adenocarcinoma cells (SW480). They demonstrated that AIE-75/harminon suppressed in vitro growth of these colon adenocarcinoma cells by inducing cell cycle arrest (G2/M), in correlation with its expression levels. Cell cycle arrest was accompanied with the emergence of DNA hyperploidy, due to 'mitotic slippage'. This is a spontaneous exit from prolonged mitotic arrest, followed by DNA replication without cytokinesis, resulting in hyperploid formation (7). DNA ploidy is a significant prognosticator of colon adenocarcinoma (8).

In conclusion we can state that different groups have been studying the possible correlation between germline mutations of AIE-75/harmonin as seen in Usher syndrome type 1C and human colorectal adenocarcinoma through interaction with MCC2. However prove could not yet have been delivered. Further investigations concerning this subject should be encouraged. This rare case of a young patient with no know comorbidity is the perfect example that there could be a correlation between Usher syndrome and colorectal cancer.

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