



Case Report

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Colonic Adenocarcinoma in a Patient with Velo Cardio Facial Syndrome (VCFS) and 22q11.2 Microdeletion

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Abstract

Colorectal cancer (CRC) is one of the most common cancers and second most common cause of cancer related mortality. Chromosomal instability and microsatellite instability have long been considered as major factors in the etiology of colon cancer. Chromosome 22q losses have been reported both in primary and metastatic CRC. Chromosome 22q11.2 microdeletion syndrome is an umbrella term that encompasses various phenotypes, and is the most common microdeletion syndrome in humans. We report an uncommon association of colon cancer in a patient with VCFS and 22q11.2 microdeletion. While this finding may be coincidental, it is important to further evaluate patients with CRC and 22q11.2 microdeletion to assess if this association is more frequent than has been reported.

Keywords

Colorectal cancer; Velo cardio facial syndrome; Chromosome 22q deletion

Introduction

CRC is the third most common cancer and the second most frequent cause of cancer death [1]. Molecular alterations in CRC can be broadly classified into 2 groups: chromosomal instability and microsatellite instability. Chromosomal instability can be in the form of aneuploidy or chromosome rearrangements which can lead to inactivation of tumor suppressor genes and/or activation of oncogenes [2]. The loss of heterozygosity (LOH) of tumor suppressor genes is suggested to be one of the most important steps in the carcinogenesis of CRC. LOH, the loss of one allele at a specific locus, is caused by deletion, mutation or loss of the entire chromosome. Multiple recurrent chromosomal abnormalities including 22q deletions have been reported in both primary and metastatic CRC [3]. In CRC, allelic loss at 22q has been reported with a frequency of 20-30% [4].

The 22q11 microdeletion syndrome is one of the most common microdeletions in humans with an estimated incidence of 1 in 2000 to 6395 newborns. However, this estimate is considered to be

artificially low due to under-diagnosis because of extreme clinical heterogeneity associated with this syndrome [5-8]. The phenotype associated with this 22q11 deletion syndrome is broad and includes facial dysmorphism, congenital cardiac defects, velopharyngeal insufficiency with or without cleft palate, thymic hypoplasia, immune deficiency, parathyroid hypoplasia, developmental delay, learning disabilities, psychiatric disorders, renal, ocular and skeletal malformations and hearing loss. As adults the main presenting symptoms are developmental delay, cardiac anomalies, psychiatric disorders, and early on-set Parkinson's disease [9]. Although one of the features of 22q11 deletion syndrome is immune deficiency, there are only rare reports of associations between 22q11 deletion and specific malignancies. Here we report such an association with colorectal cancer which was never reported before.

Material and Methods

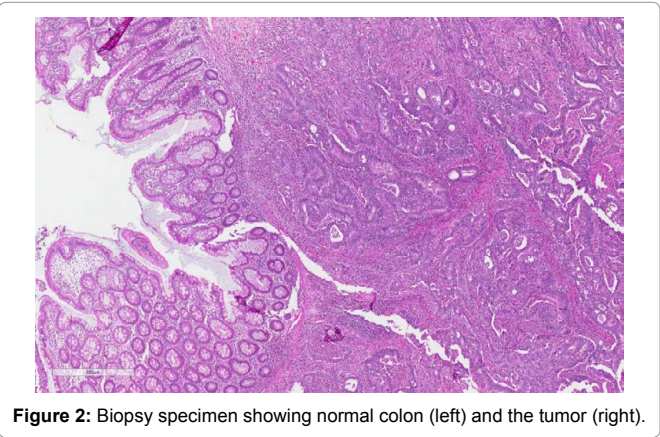
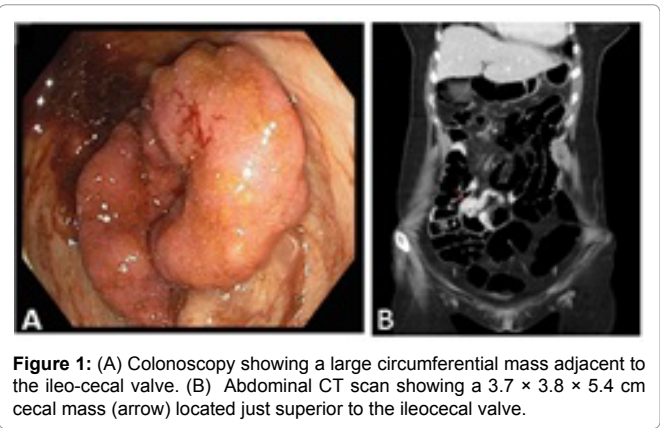
Case report

A 31-year-old female with VCFS, was admitted with symptomatic anemia which required blood transfusion. Her previous medical history was significant for cleft palate and Tetralogy of Fallot, both of which were surgically repaired, and laparoscopic cholecystectomy for symptomatic gallstones in 2012. She had previously developed an aneurysm of the pulmonary artery which eroded into the sternum that required another cardiac surgery with replacement of the pulmonary valve and reconstruction of the sternum. She also received a course of growth hormone for failure to thrive in her childhood. On physical exam she had distinctive facial characteristics consistent with the history of VCFS and cleft palate. Her abdomen was soft and non-distended. Rectal exam revealed bright red blood. Subsequent colonoscopy showed a nearly obstructive mass located in the ascending colon just above the ileocecal valve (Figure 1A). CEA was 14.7. Preoperative CT scan of the chest and abdomen were consistent with cecal mass and mild mesenteric lymphadenopathy (Figure 1B). She underwent an open right hemicolectomy with ileotransversoanastomosis. Postoperative period was complicated by superficial surgical site infection that required removal of the staples from the wound to ensure wide drainage of a small infected hematoma. Otherwise, she recovered well and was discharged home on post-operative day 6. She was evaluated by the Medical Oncology service and adjuvant chemotherapy was not recommended. Subsequent colonoscopy, CT scans, and CEA were normal. She continued to follow with oncology team with no signs of cancer recurrence.

The excised tumor specimen contained ileum and right colon, measuring 14.5 cm in overall length and 6.5 cm in circumference. Opening of the colon revealed an exophytic mass measuring 5.9 × 4.8 × 2.4 cm that is 3.5 cm from the proximal ileal margin and 9.5 cm from the distal colonic margin. The tumor was grossly 3.0 cm from the nearest mesenteric margin. The serosal surface was grossly intact without papillary excrescences penetrating tumor or adhesions. Cross-sectioning of the mass revealed invasive tumor grossly extending to the serosa but not through. Tumor invaded through the muscularis propria into the subserosal adipose tissue or the non-peritonealized pericolic or perirectal soft tissues but did not extend to the serosal surface (Figure 2). No lymphovascular invasion

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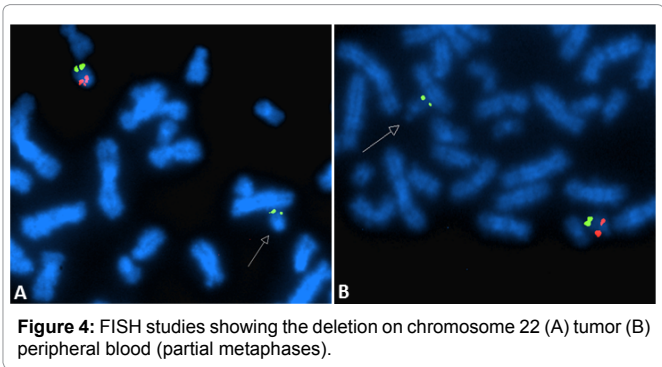
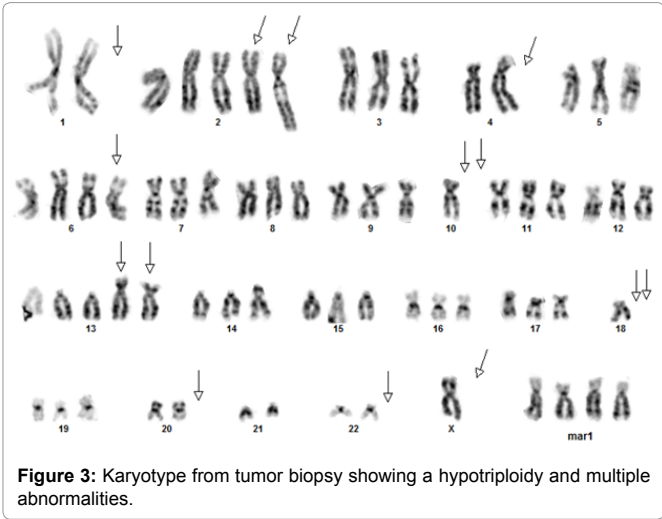
was observed as 14 resected lymph nodes were benign based on the pathological evaluation. Based on these findings, a diagnosis of moderately differentiated colonic adenocarcinoma was made with a TNM stage pT3 NO MX (stage IIA). Chromosome analysis from both the tumor biopsy and peripheral blood was carried out using standard protocols. Analysis of 20 G-banded metaphases from the tumor showed a complex hypotriploid karyotype in 11 cells while the remaining 9 cells showed a normal karyotype. The abnormal cells with hypotriploid karyotype had multiple numerical and structural abnormalities including a homogeneously staining region (HSR) on chromosome 2q and multiple unidentified marker chromosomes (Figure 3). Fluorescence *in situ* hybridization (FISH) studies with 22q11.2 microdeletion critical region (Cytocell, Windsor, CT) on the tumor as well as the peripheral blood sample showed a deletion consistent with the patient’s known diagnosis of 22q11.2 microdeletion (Figure 4A and B). Molecular studies on the peripheral blood sample for microsatellite instability including the PMS2, PMS2, MLH1, MSH2, MSH6, EPCAM loci showed no pathogenic mutations, variants of unknown significance, or gross deletions or duplications.

Discussion

Human chromosome 22 is one of the smallest chromosomes in the genome spanning 51 Mb and contains about 855 annotated genes [10], however, chromosome 22 contributes disproportionately to the human morbidity. Several genomic disorders and cancers have been associated with this chromosome; the most common of these being the 22q11.2 microdeletion syndrome, the Philadelphia chromosome in CML, and several loci linked to autism and neuropsychiatric

disorders and soft tissue sarcomas. One of the reasons for such high frequency of genomic alterations on this chromosome is attributed to its architecture in terms of low copy repeats (LCRs). These LCRs are known to mediate the common 3 Mb deletion seen in majority of the patients with 22q11.2 microdeletion syndrome. However, rare deletions spanning larger genomic segments on 22q have been reported and such deletions are shown to be mediated by LCRs A through H [11].

Checkpoint kinase 2 (*CHEK2*) gene on chromosome 22q12.1 is identified recently as a breast cancer susceptibility gene [12,13] and some germ-line variants of this gene have been reported to increase the risk of colorectal, thyroid, prostate and kidney cancer in specific populations [14,15]. Although the extent of the 22q11.2 deletion in our patient is not known and the most common deletion associated with VCFS is 3 Mb in size, given the reported existence of large deletions involving this region on proximal 22q, it is possible that the deletion may involve the *CHEK2* gene in our patient. Further studies to characterize the extent of deletion in our patient could elucidate if the *CHEK2* gene has any pathogenic role in our patient’s CRC. On the other hand, distal 22q13 deletion resulting in LOH have been found in high frequency (>35%) and reportedly involve more than 30 loci [16]. Based on these studies, it was suggested that there are 2 regions of LOH on chromosome 22 that confer adverse prognosis in terms of progression and metastasis in CRC [17]. These 2 reported minimal deletion regions, the first region being located between markers D22S1171 and D22S274 and the second flanked by markers D22S1160 and D22S1149 [17], are much more distal to the 22q11.2



microdeletion observed in our patient and thus the prognostic significance of this more common proximal deletion resulting in the most common genomic disorder is not known. Since these two regions of LOH on distal 22q13 are associated with CRC progression and metastasis, and our patient's deletion did not extend to this region may confer good prognosis in our case. This observation can be further supported by the clinical outcome of our patient who continues to be in remission as of this time.

The chromosome abnormality observed in our patient most probably represents a coincidental finding. However, given the involvement of chromosome 22, especially the proximal regions 22q11.2, 22q12 and 22q13 in CRC, it is prudent to monitor patients with either of these conditions to assess increased risk if any.

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