Synchronous Dual Primary Malignancies of Liver and Pancreas with Colonic Metastasis: An Unique Presentation

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Abstract
Synchronous appearance of the primary gastrointestinal malignancies is rare. Coexistence of primary pancreatic and hepatocellular carcinoma as synchronous malignancy is even rarer. We report a case of such combination in a 50 year old female who presented with bleeding per rectum and while evaluating we found simultaneous appearance of primary malignancies of pancreas, liver and solitary colonic metastasis from the pancreas in the background of chronic calcific pancreatitis. To the best of our knowledge this combination of synchronous pancreatic and hepatocellular carcinoma and colonic metastasis from the pancreas is unique.

Introduction
The frequency of multiple primary tumors among all cases of malignancy has been reported as 1 to 3%.¹ Occurrence of the multiple primary cancers is rare; however their suspicion and detection may lead to the benefit of terminally ill patients. Study of multiple synchronous primary cancers is important to provide insight of a shared genetic basis and to detect patients at risk for second malignancy. As the use of more sophisticated diagnostic and imaging modalities is increasing the rate of detection of multiple primary cancers is also increasing. We report a unique combination of the occurrence of the synchronous dual malignancy of gastrointestinal tract with rare colonic metastasis from the primary pancreatic carcinoma.

Case Report
50 year old female patient presented to our institute with history of abdominal pain, weight loss, bleeding per rectum intermittently. There were no cardio-respiratory complaints. Past history was significant for diabetes mellitus. She was cachexic and pale. Chest was clear, ascites was present and there was no organomegaly. There was no lump or external stigmata of the familial cancer syndromes. Investigations revealed normocytic hypochromic anemia (Hb. 8.2 gm%), low Serum Ascites - Albumin Globulin (SAAG) gradient, negative viral markers (HIV, HBsAg, anti-HCV), and stool for occult blood was positive. Fasting blood sugar was 228 mg/dl. Serum amylase and lipase were normal. Ascitic fluid was negative for malignant cells and ascitic amylase was normal. X-ray abdomen showed extensive pancreatic calcifications (Figure 1c). Upper GI scopy was normal. Ultrasound of the abdomen revealed thickening of the distal colonic wall and hypoechoic lesion in liver of size 2 x 1.5 cm in right lobe. Colonoscopy showed submucosal bulge of size 2 x 2 cm in the sigmoid colon with small overlying ulcer; biopsy revealed submucosal deposits of adenocarcinoma (Figure 2a). Triple phase CT scan of the abdomen revealed multiple, ill-defined, heterogeneous moderately peripherally enhancing lesion of varying sizes in both lobes of liver, largest of size 1.9 x 1.5 cm noted involving segment IV with arterial enhancement and venous washout. Pancreas was atrophic with multiple intra-parenchymal and intraductal calcifications. A single ill-defined hypodense peripherally enhancing lesion of size 3.9 x 3.0 x 2 cm was noted...
Fig. 2: (a) Sigmoid biopsy: 10x HandE tumor tissue showing submucosal deposits of adenocarcinoma (b) Pancreatic FNAC: 40x HandE-cells are showing round to ovoid nuclei with variable amount of cytoplasm consistent with adenocarcinoma (C) Liver FNAC: 10x, HandE- sheet of tumor cells with scattered lymphocytes and bare tumor nuclei. (d). Liver FNAC: Oil immersion, HandE- binucleated tumor cell with intranuclear inclusion s/o well differentiated hepatocellular carcinoma

Fig. 3: Immunohistochemistry of the sigmoid colonic Biopsy: the tumor cells express CK-7, CA19-9 and CDX2 and are negative for CK20

MPCs (Multiple primary cancers (MPC) are uncommon. In a study by Németh et al, dual malignancies were seen in 3-5% of patients, triple tumors occur in only 0.5%, and quadruple tumors in 0.3%. Pancreatic cancers are very aggressive in their natural course. The overall survival rate of advanced pancreatic cancer cases is < 5% at five years with most patients dying within the first year. Pancreatic cancer commonly spreads to the liver, lungs, abdomen, regional lymph nodes and peritoneum. However only four cases of solitary colonic metastasis from pancreatic carcinoma have been reported till date. Specific immunohistochemical (IHC) staining is useful to diagnose site of primary tumor in colonic metastasis. Serum CA19-9 is the useful biomarker for pancreatic cancer. Unfortunately serum CA19-9 level estimation in pancreatic cancer is limited by poor sensitivity, false negative results in lewis negative phenotype (5-10%). This might explain the low value of serum CA19-9 as found in our case.

Cytokeratin (CK) is an intermediate filament protein; (CK) 7 is expressed in epithelial cells of the kidney, prostate, pancreas, ovary, lung, and breast, but not in the colon or gastrointestinal tract. However, CK 20 is expressed in all cases of colorectal carcinomas, 62% of pancreatic carcinoma cases, and 50% of gastric adenocarcinomas. CK7 positivity and CK20 negativity (as in our case) helped to identify the primary tumor. Although the mechanisms involved in the development of multiple primary cancers are not fully understood, several factors have been implicated. These findings are complex, and include environmental factors (tobacco and alcohol abuse, occupation, and pollution), genetic predisposition, previous medical treatment (radio- or chemotherapy), gender-specific factors, hormonal factors, and interaction of these factors. The principle difficulty in diagnosing multiple primary cancers is to differentiate it from the metastasis. Warren’s and Gates criteria for multiple primary malignant tumors mandates tumors occurring at different locations must be histologically malignant and separated by normal mucosa and each tumor must not be a metastasis involving tail of pancreas (Figure 1a, b). Endoscopic ultrasound showed hypoechoic lesion in the tail of pancreas (Figure 1d). EUS-FNA from this lesion was suggestive of adenocarcinoma (Figure 2b). Suspecting the possibility of synchronous malignancies we did FNA from the liver lesion which showed well differentiated hepatocellular carcinoma (Figure 2c, d). To differentiate the liver lesion from metastasis we did serum alpha fetoprotein (AFP) which was high (541ng/ml). Serum CA19-9 was within the normal range. Immunohistochemistry of colonic lesion showed CK7, CA 19-9, CDx (dim) immunopositivity and CK 20 immunonegativity (Figure 3), confirming origin of colonic metastasis from pancreatic cancer. Patient was not affording for the further workup.

Discussion

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of another. Moertel proposed that two primary tumors found within 6 months could be defined as synchronous, otherwise (more than 6 months) as metachronous. Most commonly reported synchronous gastrointestinal malignancies are colonic-non-melanoma skin cancer and colonic-kidney malignancies. The first Indian case report of dual malignancy involving pancreas and liver was reported in 2014. The frequency of pancreatic cancer in association with cancer of other organs is estimated to range from 1% to 20% with malignancies predominately of the stomach, colon, thyroid and genitourinary tract. Occurrence of colonic metastasis in association with cancer of other organs like pancreas is rarely reported. The prognosis of patients with multiple primary malignancies should be determined independently by the stage of each malignancy. For treatment purpose most aggressive and advanced cancer is to be addressed first. Patients with pancreatic cancer have a relatively short survival time; second primary cancer is hence rarely detected.

**Conclusion**

Investigation of patients with multiple primaries and their families might lead to the identification of predisposing gene defects. At least we should think the possibility of occurrence of synchronous / metachronous malignancy in patients with pancreatic carcinoma. Prognosis of patients with dual synchronous cancers including pancreatic cancer mainly depends on the prognosis of the pancreatic malignancy. Many familial cancer syndromes are well-defined. Our case had no evident family history of cancer; it is probably sporadic occurrence of MPC.

**References**