

SPREADING OF A COLON ADENOMA: A CASE REPORT

Domenico Macaluso¹, Italia F² and Bianciardi G³

¹Domenico Macaluso, Endoscopy Service, Ribera's Hospital, Agrigento, Italy

²Fabrizio Italia, Laboratory of Pathology "OncoPath", Augusta, Siracusa, Italy

³Giorgio Bianciardi, Department of Medical Biotechnologies, Pathologic Anatomy, Siena University, Italy

The capacity to spread beyond the limits of the tissue in which it was originated and to survive is the prerogative of malignant tumors, the feature at the basis of the concept of malignancy. In 90% of cases, a colon cancer originates from its dysplastic precursor, the adenomatous polyp; evidence that 60-70% of that cancer is localized in the distal colon suggests that environmental factors affect the progression of the tumor, like the activation of HIF-1 transcription factor and the physiological hypoxia that exists in this environment. Here we describe the finding of a clinical case where a benign tubulovillous adenoma appears able to survive and colonize the colonic mucosa away from the primary lesion. It was supported by visual inspection, histological evidence and fractal analysis (each tested morphometrical parameters- box dimension, information dimension, mass dimension, perimeter-area dimension, algorithmic complexity- overlapped each other, $p < 0.03$). If this finding will be confirmed in a high number of patients and by experimental studies, the current diagnostic/therapeutic approaches of the colon tumors should be modified, not only regarding colorectal adenomas, but also the superficial cancer of the large bowel. The mechanisms of spread of a malignant tumor in other tissues (metastasis) are well known since the previous century (bloodstream, lymphatic circulation, contiguity, via transcelomatic dissemination). It is a process affected by many factors, like as the ability to overcome hypoxia and to be provided with a vascular network. During a colonoscopy, two benign lesions (adenomas, one large vegetating proximal lesion and one small lesion, distally) were revealed in a patient, the position and the aspect at gross and microscopic level suggesting that the small lesion could be derived from the other. In this work we face a clinical case that may suggest the possibility of an adenomatous polyp, a benign tumor, to spread and colonize the colonic mucosa remotely, with mechanisms considered, so far, prerogative of a malignant tumor.

Case report: During a colonoscopy performed at the Ribera's Hospital Endoscopy Service (Provincial Health Institution of Agrigento, Sicily) in a 63-year-old male that came to our attention for a positive Fecal Occult Blood Test (FOBT). Colonoscopy (Pentax EPM-3000 colonoscope) demonstrated the presence of two eteroplastic lesions:

1. Near the cecum, the presence of a large vegetating lesion, dysplastic, lumpy but not ulcerated, with a short and thick peduncle; it invaded the intestinal lumen and occupied the entire whole of it.
2. Approximately 20 cm distal to the above lesion, a small eteroplastic lesion located just below the hepatic flexure, lying on a colonic haustra. The mass, approximately 3 mm in diameter, was anchored to the colon mucosa through thin threadlike structures, and in relation with blood capillaries.

The structure hadn't a vascular pole and at the detachment from the mucosa, the tumor appeared without a peduncle; capillaries, breaking away from the lumen of the colon, giving rise to a modest bleeding. It was not possible to proceed with endoscopic resection due to the high dimension of the first lesion, and it was decided to perform some biopsies for histological/histomorphometric evaluations. In the present study, we describe a clinical case where a benign adenoma appears able to survive and colonize the colonic mucosa away from the primary lesion. This was supported by visual inspection during colonoscopy (presence of a small mass, distally to a large vegetating lesion; it was without a peduncle, vascular axis and vascular pole, anchored to the colon mucosa through thin threadlike structures, and in relation with nest of capillaries), histological evidence (the same microstructure of a tubulovillous adenoma with low-grade epithelial dysplasia and notes of dyskaryosis) and fractal analysis (five fractal parameters, obtained by analyzing about 1500 microstructures for each lesion, perfectly overlapped between the lesions). The small distal adenoma appears to be the daughter of the large vegetating proximal lesion. The Warburg effect, known since 1956, is the ability of cancer cells to respond to

hypoxia, with an adaptation of their energy cycle. The colon mucosa is an anoxic environment, where a lot of different microaerophilic bacteria and archaeobacteria live. This could be a crucial step in the survival of that colonic neoplastic embolus, survival and adaptation being permitted by that anoxic environment. A key role should be played by the mitochondrial protein TRAP-1, with its ability to intervene on the transcription factor HIF-1 levels. In normoxic conditions, this mediator is degraded by hydroxylation, whereas in neoplastic tissues TRAP-1 stabilizes HIF-1. In effect, immune histochemical investigations have shown that in malignant tumors there are significant high levels of HIF-1 in comparison to healthy tissues and if a metastatic process is present, still higher HIF-1 levels are present. In this context, a kind of natural selection will favor the growth of the cellular clone adapted to the hypoxic stress. We can recall that HIF-1 is a potent stimulator mitogen, specific for endothelial cells; it produces changes of cellular metabolism, triggering the activation of glycolytic enzymes; leading angiogenesis and neovascularization, through vascular endothelial growth factor activation. Significant should be also the role of nitric oxide, involved in the tone regulation of the newly formed vessels. If our finding will be confirmed in a high number of patients, the current orientation to treat sessile adenomas of the colon by means of endoscopic sub-mucosal dissection must be revised. There is no doubt that early diagnosis of adenomatous polyps and their removal by endoscopic resection reduces the incidence of the colon carcinoma, but we must prevent the fragmentation of the polyp. Otherwise, the resection of the tumor could produce the primum movens of an iatrogenic spread of a colonic adenoma, due to the particular morphological characteristics of the colonic mucosa (folds, diverticula) and the presence of an anoxic environment. Even the slow intestinal transit, an increasing condition for the actual lifestyle, could help the engraftment of such adenomatous embolus. A dangerous situation for the patient, being the adenoma a benign lesion that can evolve in a malignant lesion. Moreover, it may be also true for a superficial colon cancer, if treated by resection or endoscopic dissection: the residual fragments could be able to colonize contiguous or distal areas resulting in repetitive carcinomas. Experimental studies might confirm our hypothesis. One should be carried out on cre-recombinase genetically modified mice, characterized by a higher incidence of tumors in the distal colon. The experimental procedure should be obtained by taking tumor fragments from a proximal area of the colon and implant them by contact in the most distal areas, and then analyze the survival, engraftment and development of the cell aggregates. Another experimental procedure could be performed dosing HIF-1 levels in humans, checking its values in comparison to the pO₂ levels and dysplasia degree in different parts of the colon."

BIOGRAPHY

Domenico Macaluso is a surgeon and an endoscopist. He graduated in Palermo (Sicily) and is responsible for Digestive Endoscopy of the Hospital Presidium of Ribera (Agrigento). He also has a qualification of Rescue Diver and has coordinated several underwater researches in the Mediterranean, in the hypoxic basins of the oceanic ditches. He compared the methanogenic bacterial flora of the hypoxic marine basins, with the methanogenic bacteria of the intestinal microbiota and he collaborates with the Department of Biotechnology of the University of Siena, on the study of the probable capacity of colon adenomas, to propagate at a distance, a phenomenon that is probably mediated by the physiological intraluminal hypoxic environment of the colon."

mimmomac57@gmail.com