Abstract. Spontaneous remissions have been reported in solid tumors such as melanoma and renal cell cancer. However, spontaneous remissions in colon cancer have not been previously radiographically confirmed. A case of colon cancer metastatic to the retroperitoneal lymph nodes that exhibited a durable spontaneous regression is reported. The exact trigger of this phenomenon has not been elucidated; however, an antitumor immune response is the most likely explanation. The identification and characterization of similar cases would probably result in defining a patient population that can be followed by observation and may result in the development of novel therapeutic strategies.

Colorectal cancer (CRC) is the third most commonly diagnosed and the second most common cause of cancer death in the United States. It is estimated that in 2008, 148,181 new patients would be diagnosed with CRC, of whom more, approximately 49,960, would die of their disease (1).

A steady increase in the median survival for stage IV CRC has been observed over the last decade with the introduction of new chemotherapy and targeted agents (2-7). The treatment of unresectable metastatic CRC with chemotherapy is typically advised until disease progression. Stop-and-go approaches have been investigated, but recent evidence has suggested the possible inferiority of regimens incorporating extended chemotherapy breaks (8). It is generally accepted, however, that patients with complete clinical responses may discontinue chemotherapy until radiographic evidence of disease recurrence emerges (9). Although the overwhelming evidence supports the use of chemotherapy in metastatic CRC, a subpopulation with indolent disease probably exists, where observation may not be unreasonable. This is suggested by the small, but real, percentage of patients who have prolonged stable disease on non-chemotherapy best supportive care arms on clinical trials (10, 11). It is not clear if these stabilizations are related to a slow growing cancer, a host immune response, or both. Given the lack of prior documented spontaneous CRC remissions, a robust innate immunological antitumor activity in stage IV cancer has been previously excluded. The first case, in the modern era, of a radiographically confirmed spontaneous CRC regression, suggesting an innate antitumor host response is presented.

Case Report

An 86-year-old Caucasian female presented to the Roswell Park Cancer Institute in January 2005 for treatment recommendations following a right hemicolectomy. Her pathology review confirmed a T3N0 (stage II) adenocarcinoma (Figure 1) with nine lymph nodes evaluated. The malignant glands were surrounded by a dense infiltrate. It was difficult to be certain if this infiltrate was elicited directly by tumor cell antigens or indirectly by damage caused to the tissue as the tumor invaded through the stroma. Computed tomography (CT) scans of the chest, abdomen and pelvis did not show any metastatic disease. She was recommended surveillance without any adjuvant chemotherapy. Eight months following her hemicolectomy, in April 2005, a CT scan revealed enlarged retroperitoneal and aortocaval lymph nodes. The patient declined any possible chemotherapy at that time and thus watchful waiting with serial CT scans was advised. Six months later, her left aortocaval lymph node was found to be slightly enlarged. Further serial CT scans showed ongoing slowly progressive disease. By April 2006, her retroperitoneal lymph node measured 3×2.4 cm and her left aortocaval node measured 2.5×1.7 cm (Figure 2). Uptake was confirmed on positron-emission tomography (PET) scan, suggesting metastatic disease. Capecitabine (Xeloda®) monotherapy was discussed with the patient, but given the slow rate of growth of the tumor, she elected to continue with observation. Surprisingly, a CT scan conducted three months later in July 2006 showed the retroperitoneal lymph node to have decreased in size to 2×1.6 cm and that of the left aortocaval lymph node to...
1.8×1.2 cm (Figure 3). The spontaneous regression was postulated to be due to atypical inflammation vs. low-grade lymphoma and observation was advised. A repeat CT scan, 6 months later in January 2007, showed an increase in size of the retroperitoneal lymph node to 2.5×1.9 cm and of the aortocaval lymph node to 2.9×2.2 cm (Figure 4). A CT guided lymph node biopsy was performed and confirmed a poorly differentiated adenocarcinoma, similar to her original colonic adenocarcinoma (Figure 5). At her request, no treatment was initiated and a repeat CT was performed again in May 2007. This showed a further decrease in the left periaortic node size to 1.2 cm (Figure 6). The patient continues to be followed by observation without any chemotherapy treatments.

**Discussion**

The spontaneous resolution of colonic polyps has been reported in patients with familial colonic polyposis. Sixty-four percent of patients with familial polyposis had some spontaneous regression of their polyps in a study published by Feinberg et al. (12). This has been confirmed in other reports (13, 14). Spontaneous regressions have also been reported in patients with renal cancer (15) and melanoma (16, 17). The cause of regression in those cases was postulated to be secondary to an antitumor immune response. Other epithelial carcinomas have rarely been associated with spontaneous remission; a few cases in lung cancer and gastrointestinal malignancies have been reported (18-20, 21). To our knowledge, only three cases of spontaneous regression of colon cancer have been reported in the past (22-24). None of the regressions were confirmed by CT scans. In the present case, the radiologically-confirmed regression occurred on two occasions and was not triggered by any conventional chemotherapy or unconventional treatments. The patient was not receiving any over-the-counter medicine, supplements or vitamins. She did not have any known chronic illnesses or autoimmune diseases.

The etiology of the spontaneous regression is unclear in this case. An immune-mediated response cannot be ruled out nor confirmed. An immune-mediated antitumor response has been described in pre-clinical CRC in *in vivo* models. Miyamoto et al. (25) reported the presence of primary colon cancer regression in the WF Osaka rat strain. The regression rate was most significant (40%) for stages I and II colon cancer. Macrophage infiltration and central tumor necrosis in these cases suggested an immune-mediated response. The same group reported similar findings in the highly inbred Wistar Furth rat (26). In the present case, there was a dense lymphoplasmacytic infiltration in the primary tumor, which may suggest that an immune response was being mounted against this particular tumor. This could not be confirmed in the metastatic biopsy, partly because of the natural presence of lymphocytes in the lymph nodes.

To conclude, this case confirms the possibility of spontaneous regression of metastatic CRC. The detailed molecular and immunological investigation of such cases may result in the identification of a small subgroup of patients that could be followed by observation and may also result in the identification of novel pathways to target metastatic CRC.
References


Figure 3. Retroperitoneal lymph node 2x1.6 cm and left aortocaval lymph node 1.8x1.2 cm (24/7/06).

Figure 5. Colorectal adenocarcinoma metastatic to a lymph node. Needle core biopsy of a lymph node. Residual nodal lymphocytes can be seen in the center and extending into the lower right corner of the picture. Metastatic carcinoma is seen in the center and upper left corner. (Magnification x200).

Figure 4. Retroperitoneal lymph node to 2.5x1.9 cm and of aortocaval lymph node 2.9x2.2 cm (16/1/07).

Figure 6. Left periaortic node 1.2 cm. Retroperitoneal node 2.5x2.1 cm (9/5/07).


Received July 26, 2008
Revised December 8, 2008
Accepted December 15, 2008