CASE REPORT

α-Foetoprotein–producing Primary Rectal Adenocarcinoma

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ABSTRACT

This report is of a 44-year-old woman with an α-foetoprotein–producing rectal adenocarcinoma. At presentation, her serum α-foetoprotein was 158,334 μg/L, and investigation excluded other causes, such as gynaecological malignancy, hepatocellular carcinoma, germ cell tumour, or hepatoid adenocarcinoma. The patient developed early distant metastasis despite treatment with 5-fluorouracil-based chemoradiotherapy. Further chemotherapy with 5-fluorouracil, irinotecan, and oxaliplatin plus bevacizumab resulted in radiologically stable primary tumour and liver metastases 12 months after treatment.

Key Words: Adenocarcinoma; alpha-Fetoproteins; Antineoplastic combined chemotherapy protocols; Combined modality therapy; Rectal neoplasms

INTRODUCTION

α-Foetoprotein (AFP) is a marker for hepatocellular and germ cell (non-seminoma) carcinoma. AFP is a glycoprotein produced in large amounts during foetal life and is homologous to albumin. In healthy adults, <10 μg/L of AFP is found in the circulation. AFP is elevated during pregnancy, and in association with benign liver disease (hepatitis, cirrhosis) and some cancers; increased AFP production in neoplasms of the stomach, pancreas, bile duct, and lung have been reported.[1] However, AFP production due to rectal cancer is rare, and there have been only a few patients in whom the serum AFP level was >1000 μg/L. This report is of a patient with primary rectal adenocarcinoma who presented with a serum AFP level of 158,334 μg/L.

CASE REPORT

A 44-year-old woman presented in 2007 with a history of loose stools for 6 months, accompanied by occasional episodes of bleeding. Colonoscopy performed at a local hospital revealed a mass in the rectum 5 cm above the anal verge, and biopsy showed dysplasia with focal invasion.

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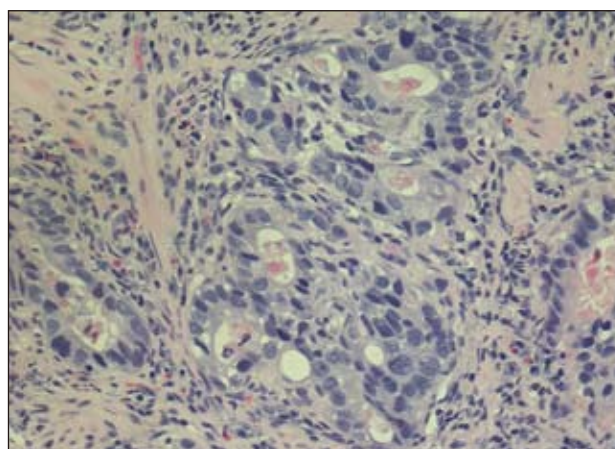*E-mail: rashmi.koul@saskcancer.ca*

Figure 1. Adenocarcinoma of the rectum with well-formed glands and normal colonic mucosa highlighting severe tumour necrosis and acute inflammation (haematoxylin and eosin stain; original magnification, x 100).

The patient was referred to the Department of Radiation Oncology, Allen Blair Cancer Center, Regina, Canada, where repeat colonoscopy showed a 6-cm annular constricting tumour 7 cm above the anal verge, and biopsy showed invasive poorly differentiated adenocarcinoma associated with severe tumour necrosis and acute inflammation. Well-formed glands were present, with a portion of normal colonic mucosa (Figure 1). The tumour cells were negative for cytokeratin (CK) 7, CK20, and carcinoembryonic antigen (CEA), but showed focal positivity for AFP (Figure 2) and caudal-related homeobox transcription factor 2 (CDX 2) [Figure 3].
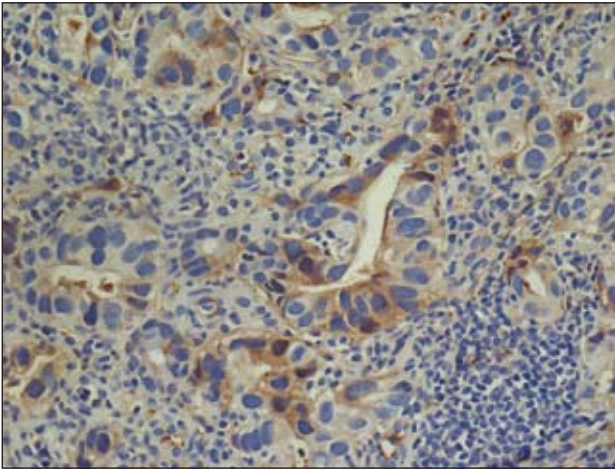
Figure 2. Immunoperoxidase stain showing positive α-foetoprotein in rectal biopsy (original magnification, x 100).
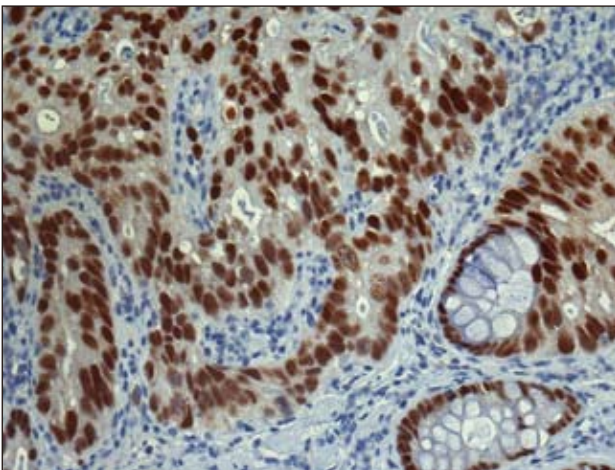

Figure 3. Immunohistochemical stain showing positive CDX2, specific for colonic adenocarcinoma (CDX2 antibody marker; original magnification, x 100).

Computed tomography (CT) scan of the pelvis demonstrated a large bulky mass, approximately 10 cm in diameter, in the pelvic cavity between the uterus and the rectum. The mass was heterogeneous in nature and was associated with bilateral hydronephrosis and satellite nodules in the pelvis. There was a small mass in the right ovary. No liver metastases or primary liver lesion was evident, and there were no signs of cirrhosis. The lungs were clear.

The patient underwent magnetic resonance imaging (MRI) of the pelvis to delineate whether the tumour originated from the right ovary or the adjacent rectal wall. MRI confirmed the presence of a central pelvic mass, 12.2 x 10.3 x 8.7 cm in dimension (Figure 4). The lesion had a defined rim and had heterogeneous signal intensity. The lesion was close to the posterior aspect of the uterus and right adnexa. There was a discrete plane
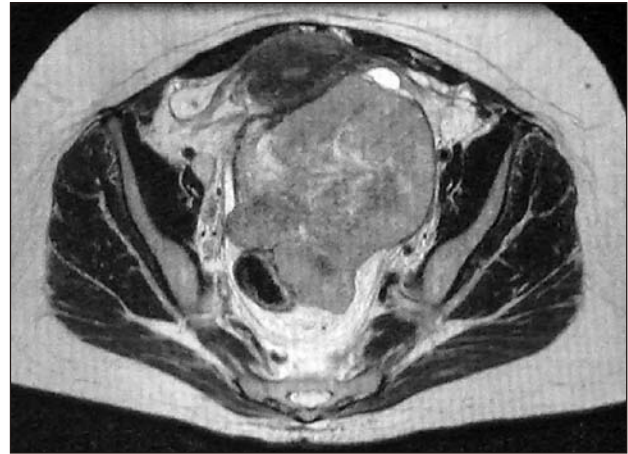

Figure 4. Pretreatment T2-weighted magnetic resonance image showing a 12.2- x 10.3- x 8.7-cm central pelvic mass intermediate to the posterior aspect of the uterus and the right adnexa. Two additional masses are seen anterior and posterior to the rectosigmoid junction.

between the uterus and the mass. The uterus was markedly displaced an-teriorly. Two additional masses were seen anterior and posterior to the rectosigmoid junction, measuring 3.4 x 2.5 cm and 3.0 x 3.6 cm, respectively. There was thickening of the colon at the rectosigmoid junction. Dilatation of the distal ureter was noted. A small amount of ascites was evident.

The patient was referred for neoadjuvant chemoradiotherapy followed by surgical assessment. Serum levels of CEA, cancer antigen (CA) 125, and β-human chorionic gonadotrophin were within the normal range, but the serum AFP level was 158,334 μg/L. Viral serology for hepatitis was negative. Due to the high serum AFP, a germ cell tumour was suspected, and other causes, such as carcinoma of the stomach, liver, or pancreas with metastasis to the pelvis, gynaecological malignancy, or hepatoid adenocarcinoma, were considered.

The patient underwent CT-guided fine needle aspiration of the pelvic mass. The aspirate contained malignant cells dispersed in dyshesive groups and individually, with large and pleomorphic nuclei, prominent nucleoli, and small-to-moderate amounts of foamy cytoplasm. Cytomorphologically, the aspirate was consistent with poorly differentiated adenocarcinoma. No features suggestive of a germ cell tumour, hepatocellular carcinoma, hepatoid adenocarcinoma, or gynaecological neoplasm were noted. 12p Chromosomal analysis did not show abnormal gene expression compatible with germ cell histology. A diagnosis of AFP-secreting adenocarcinoma of the rectum was made, although such high AFP levels from a primary rectal cancer are unusual. Her

Figure 5. Post-treatment T2-weighted magnetic resonance image showing an 8- x 7- x 6-cm mass in the pelvis consistent with a less than partial response to chemoradiotherapy.

serum AFP increased to 196,390 μg/L and the pelvic pain had worsened.

The patient was treated with neoadjuvant 5-fluorouracil–based infusional chemotherapy with concurrent pelvic external beam irradiation at a total dose of 54 Gy in 30 fractions by the shrinking field technique on an 18 MV photon machine. The patient tolerated combined treatment well. After 3 weeks of treatment, the serum AFP level decreased to 47,863.3 μg/L. Four weeks post-treatment, MRI showed a radiological response to the treatment (Figure 5). The patient was scheduled for palliative surgical debulking, but developed liver metastases within 6 weeks of finishing the chemoradiotherapy. At this point, her serum AFP was 420,826.4 μg/L. Surgical resection was cancelled, and she was given 6 cycles of 5-fluorouracil, irinotecan, and oxaliplatin with bevacizumab as second-line chemotherapy.

After 12 months, the patient is reasonably well, and the pelvic mass and liver metastases are radiologically stable. However, her serum AFP was 335,890.0 μg/L at the last follow-up.

DISCUSSION

AFP is a normal foetal serum protein that is synthesised by the liver, yolk sac, and gastrointestinal tract and shares sequence homology with albumin. AFP is a major component of foetal plasma, reaching a peak concentration of 30 μg/L at 12 weeks of gestation. Following birth, AFP clears rapidly from the circulation, having a half life of 3.5 days, and its concentration in adult serum is <20 μg/L. It is well known that serum AFP is elevated in liver tumours, especially hepatocellular carcinoma.[2] When patients with both colorectal

and liver tumours have elevated AFP, it is difficult to distinguish colorectal cancer from liver metastasis or coexistent colorectal and hepatocellular carcinoma. Few patients with rectal cancer with an AFP level of >1000 μg/L have been reported, and this patient is the first to be reported with rectal cancer and serum AFP levels of >100,000 μg/L. The rectal biopsy was typical of adenocarcinoma arising from the rectal mucosa and stained strongly positive for AFP. After excluding such possibilities as primary gastrointestinal tumour with a pelvic component, gynaecological tumour, hepatocellular carcinoma, hepatoid adenocarcinoma, and germ cell tumour, a diagnosis of an AFP-producing primary rectal adenocarcinoma was made.

Several authors have emphasised the poor outcome for these patients. However, the biological basis for the poor prognosis has not been validated or demonstrated. Sato et al reported a 43-year-old Japanese man with rectal cancer and liver metastases who had a high serum AFP level of 941 μg/L when first evaluated.[3] After 3 weeks, the serum AFP level had increased to 7060 μg/L. The patient underwent abdominoperineal excision of the rectum and biopsy of liver metastases. Immunohistochemically, AFP-positive cells were identified in both the rectal and liver tumours. Nine days postoperatively, the serum AFP level had decreased to 2000 μg/L. Despite intensive chemoimmunotherapy, the serum AFP level kept increasing, and was 267,300 μg/L 14 weeks after surgery. The patient died 3 months after surgery. The AFP doubling time was 12.8 days, indicating that a rapid doubling time may reflect the biological aggressiveness of the tumour. The mechanism may be that non-AFP–producing cancer cells convert to AFP-producing cells as the tumour progresses; it will be important to determine whether non-AFP–producing cells can transform to AFP-producing cells and the mechanisms involved.[4] However, AFP-producing colorectal tumours are rare and have poor outcomes, although the reason is not yet well understood.[5]

Kokuba et al established a rectal cancer cell line, RKK-YK, from the primary lesion of a patient with rectal cancer.[6] The transplanted tumour exhibited histological features similar to those of the primary lesion. The levels of the tumour markers CEA, CA19-9, and AFP increased in the supernatant of the culture solution and the serum of nude mice over time. Immunohistological examination of the transplanted tumour showed that anti-CEA, anti-CA19-9, and anti-AFP antibodies were positively stained. Molecular biological analysis

revealed neither point mutation nor deletion of the K-ras gene exon 1 and 2, p53 gene exon 5 to 11, or MCC. This information at the cellular level will help understanding of these types of tumours, so that more effective treatment modalities that will yield better outcomes can be developed.

Recently, bevacizumab, a humanised monoclonal antibody, has been approved for metastatic colorectal cancers. Bevacizumab is the first commercially available angiogenesis inhibitor. Bevacizumab stops tumour growth by preventing the formation of new blood vessels by targeting and inhibiting the function of a natural protein called vascular endothelial growth factor (VEGF) that stimulates new blood vessel formation.[7] Preliminary results from a large randomised clinical trial for patients with advanced colorectal cancer who had previously received treatment show that those who received bevacizumab in combination with an oxaliplatin-containing regimen, known as FOLFOX 4 (oxaliplatin, leucovorin, 5-fluorouracil), lived longer than patients who received FOLFOX 4 alone.[8] Patients receiving bevacizumab in combination with FOLFOX 4 had a median overall survival of 12.5 months compared with 10.7 months for FOLFOX 4 alone. This difference is statistically significant and corresponds to a 17% improvement in median overall survival and a 26% reduction in the risk of death (hazard ratio, 0.74).[9]

Similar results were found in a multicentre phase II study, in which bevacizumab was given in combination with FOLFOX to patients with metastatic colorectal cancer. Fifty three patients (46 with performance status 0 to 1) were enrolled.[10] Complete and partial responses were achieved for 8 patients (15.1%) and 28 patients (52.8%), respectively (overall response rate, 67.9%; 95% confidence interval, 53.8-92.0%); 11 patients (20.7%) had stable disease and 6 (11.3%) had progressive disease. With a median follow-up of 13.5 months, time-to-tumour progression was 11 months, while the median survival has not yet been reached; the probabilities of 1-, 2-,

and 3-year survival were 79.8%, 63.8%, and 58.3%, respectively. This patient also received bevacizumab, and has a good performance status and stable disease.

This report describes a rare primary rectal adenocarcinoma in a patient with a high serum AFP at presentation that had a poor outcome despite chemoradiotherapy. Newer systemic agents may achieve a better response, and their role should be further explored.

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