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Primary Colonic Cancer in Association with Schistosomiasis Japonica: A Case Report

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Summary. **An 82-year-old Japanese man with a cecal cancer and a history of Schistosoma japonicum (S. japonicum) infestation underwent ileocecal resection. In the resected specimen many heavily calcified eggs of S. japonicum were seen, distributed mainly in the submucosa adjacent to the tumor. Schistosomiasis due to S. japonicum is one of many possible contributors to the development of colorectal cancer. In this case, the 50 years between the patient's acquisition of S. japonicum and presentation with cancer may reflect unrelated spontaneous carcinogenesis, but the fact that the eggs were heavily and extensively present in the resected specimen argues for a relationship between these eggs and the cancer. Coordinating treatment for schistosomiasis with systemic follow-up to detect cancer probably would be required to establish S. japonicum eggs as a cancer promoter, the infestation of which presumably contributes to the cellular changes leading to premalignant transformation of intestinal epithelial cells.**

Key words—Schistosoma japonicum, primary colon cancer, adenocarcinoma, tumor promoter.

INTRODUCTION

Schistosomiasis due to Schistosoma japonicum (S. japonicum) is one of many possible causes of colorectal cancer, although its role is controversial.[1)] Several reports have indicated that persons with this infestation have a high mortality rate from colorectal cancer. In recent years in Japan, colorectal cancer associated with S. japonicum infestation is rare. We describe a patient undergoing resection of a primary colonic cancer who had remotely become infested with S.japonicum.

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CASE REPORT

An 82-year-old Japanese man was presented to our institution with complaints of nausea, vomiting, and sensation of abdominal distention. His past medical history was significant for cholecystectomy and choledocholithotomy 6 years previously. Intraoperatively, a whitish discoloration of the liver capsule had promoted a liver biopsy, despite the fact that the surface of the liver was not irregular. Pathologic examination of the specimen showed dilated, fibrotic portal vessels surrounded by slight lymphocytic infiltrates. Numerous S. japonicum ova, often heavily calcified, were seen at a frequency of up to some 60 ova per 0.35 m^2 microscopic field in portal areas. The liver did not microscopically exhibit cirrhotic patterns (Fig. 1).

His social history included the fact that he had been stationed in the army in China 50 years earlier during World War II. He also had been engaged in road construction in the Fuji basin in Japan in 1950s, an endemic area for S. japonica. His infestation with S. japonicum may have been acquired in either locality.

His physical examination was remarkable for abdominal distention and a firm mass palpable in the right lower abdomen. His blood examination revealed hypoprotenemia (4.8 g/dl), hypoalbuminemia (2.8 g/dl) and hypochromic anemia (red cell count was 3.2×10^6/uL, hemoglobin concentration was 8.3 g/dl). Transaminase and biliary emzyme levels were

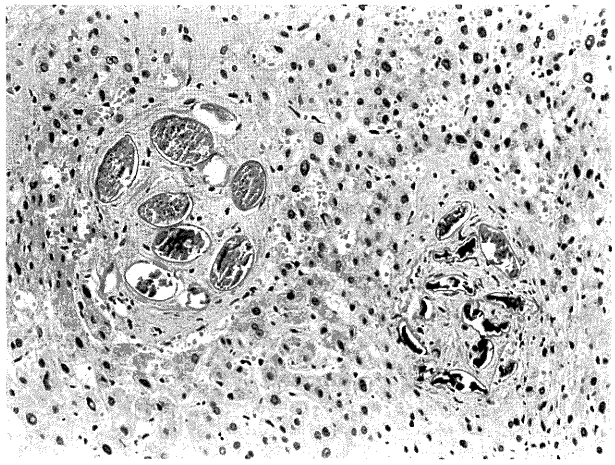

Fig. 1. Numerous ova of S. japonicum in the portal area of the liver. (H & E, ×50). The liver did not microscopically exhibit cirrhotic patterns.

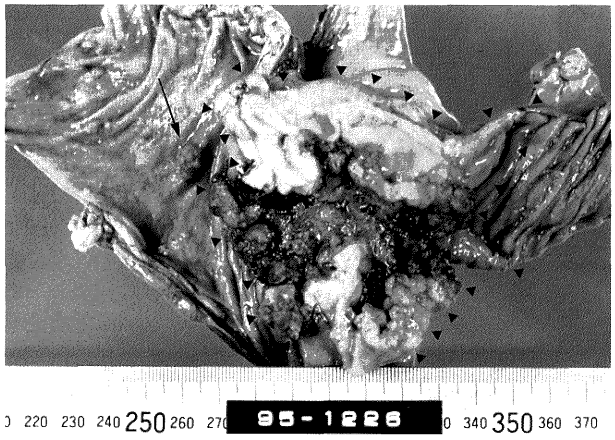

Fig. 3. The tumor in the cecum appears as an ulcerating lesion invading the terminal ileum *(arrowheads)*. A polypoid lesion was identified in the region distal the cecal cancer *(arrow)*.

almost normal, and hepatitis B antigen and antibodies against hepatitis C virus were not detected. Tumor marker levels were within the normal range. An abdominal X-P film revealed dilation of the small intestine and air-fluid levels, while a barium enema displayed a large mass measuring 6.0×8.0 cm originating in the cecum and encasing the terminal ileum (Fig. 2). Abdominal computed tomography detected multiple solid tumors, measuring 3.0 cm in the greatest dimension, in both hepatic lobes.

With a presumptive diagnosis of cecal cancer with multiple liver metastases, ileocecal resection was performed 1 month after the onset of the symptoms. The tumor surrounded the terminal ileum was pri-

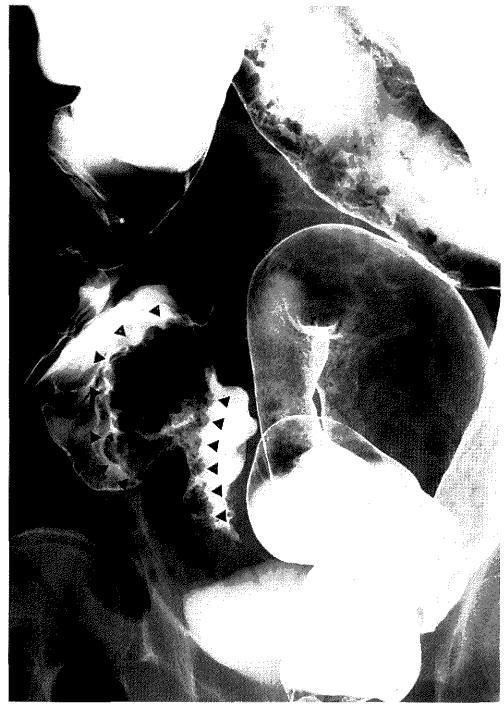

Fig. 2. Barium enema displays a large mass in the cecum which surrounds the terminal ileum *(arrowheads)*.

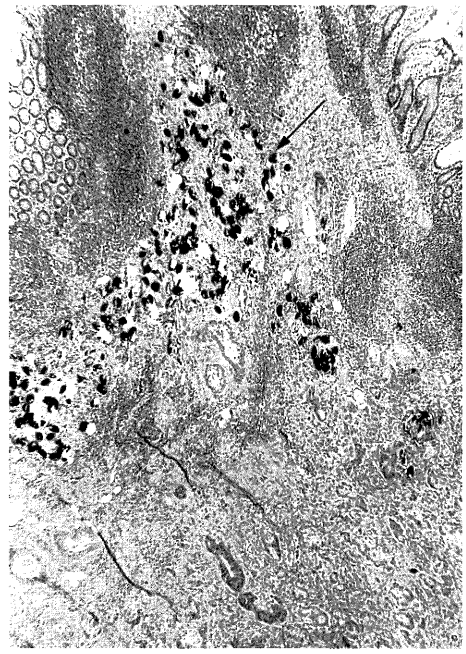

Fig. 4. The moderately differentiated adenocarcinoma contains eggs of S. japonicum. Many heavily calcified eggs can be seen in the submucosal layer surrounding the tumor *(arrow)*. (H & E, ×10)

marily located in the cecum, and invaded the retroperitoneum. Small peritoneal metastases surrounded the cecal mass. We could not reliably assess the liver tumors because of dense fibrous adhesions in the upper abdomen which was attributable to the earlier biliary surgery.

On pathologic examination, the tumor was found to be an ulcerating lesion measuring 9.0×7.0 cm. The tumor arose in the cecum and invaded the terminal ileum via the ileocecal valve (Fig. 3). A polypoid lesion measuring 1.2×1.2 cm was identified in the region distal to the cecal cancer. The tumor was staged as Dukes D (T4N2M1 or Stage IV according to the TNM system). Histopathologically, the lesion was moderately differentiated adenocarcinoma and the polypoid lesion was a tubular adenoma. Many heavily calcified eggs of S. japonicum were seen in the colonic wall surrounding the cecal cancer and the polyp, mainly in the submucosa. A few eggs were present within the cancer itself. The cecal egg deposit near the cancer was greater than elsewhere in the specimen obtained from the ileocecal resection. Nonspecific moderate inflammatory changes were observed adjacent to the cancer, including both lymphocytic and plasmacytic infiltration (Fig. 4). The inflammatory findings were comparable to those in the previous liver biopsy specimen.

The patient was discharged 2 months after the onset of the symptoms and died of hepatic failure in February 1996. No autopsy was performed.

DISCUSSION

S. japonica, considered to cause the most serious form of human schistosomiasis, is endemic in China, the Phillipines, Japan and Indonesia.[1] The present patient was stationed in China in the army during World War II. Afterwards, he had lived in an endemic area of Japan. His infestation may have been acquired in either region.

Several reports have associated both colorectal cancer and hepatic diseases with S. japonicum infestations. Schistosomiasis due to S. japonicum has been put forward as possible cause of colorectal cancer.[1] Chen et al. have reported that, among 1229 rectal biopsy and colectomy specimen obtained from patients with schistosomiasis over 24 years, 37.1% of cases had colorectal carcinoma. Conversely, among 946 specimens from colorectal cancer sections at the same hospital, 457 carcinoma (48.3%) were associated with schistosomiasis.[2]

More than half of the colorectal cancers associated with schistosomiasis have been located in the rectum or rectosigmoid area, and the frequencies of involvement of the site are higher than those in schistosomiasis nonassociated carcinoma.[2] This distribution is consistent with the predilection of sites of schistosoma egg deposits.[3] In recent years in Japan, colorectal cancer associated with Schistosoma japonicum infestation has become rare. Table 1 shows 10 clinical cases, excepting this present case, of colorectal cancer reported in the Japanese literature from 1990 to 1996.[4-13] Eight cases were located in the rectum or rectosigmoid area, and five were advanced carcinomas. The eggs were deposited mostly in the submucosa or at the base of the mucosa inside and/or outside the tumor.

In an experimental study, chronic S. japonicum infestation in ddY mice resulted in the occurrence of hepatoma in 48 out of 61 mice, and mice with S. japonicum showed higher rates of liver tumor formation in response to n-2-fluorenyl acetamide.[14] Ishii has reported that a soluble schistosoma egg antigen possesses a tumor-promoting activity, while extracts of egg and S. japonicum adult forms show no mutagenecity.[15]

Histopathologically, schistosomiasis-associated carcinoma are frequently associated with small polyps, pseudopolyps, ectopic epithelial proliferation, defects of muscularis mucosae, and multiplicity of carcinoma, whereas papillary and adenomatous polyps are not so frequent in schistosomiasis-associated carcinoma, although a true adenoma was associated in the present case. The noncancerous lesions, including the above changes, are believed to contribute to the development of colorectal carcinoma; parallels exist with carcinogenesis in ulcerative colitis.[2]

In the present case, we examined the distribution of S. japonicum eggs in the resected specimen. Many calcified eggs were seen in the submucosal layer surrounding the carcinoma, with a few eggs found in both normal mucosa and carcinoma. These findings suggest that those eggs located in the tumor fell away from the mucosal layer due to cell migration of the mucosa, accompanying the enlargement and necrosis of the tumor. While the patient's infestation with S. japonicum for 50 years may have been followed much later by coincidental cancer development, the extensive distribution of worm eggs adjacent to the cancer argues for a pathogenic relationship. Schistosomiasis may contribute to cellular changes, gradually leading to premalignant transformation of intestinal epithelial cells.

We initially demonstrated many schistosoma eggs in the patient's liver biopsy specimen. Though individuals with schistosomiasis have been studied in

Table 1. Cases of colorectal cancer associated with Schistosoma japonicum reported in Japanese literature

Patient's No.	Author and year reported (Ref. No.)	Age	Gender	Tumor site	Gross appearance	Egg distribution
1.	Morise, 1990[4]	69	M	Rectum	type 2	submucosa
2.	Shibayama, 1990[5]	65	F	Rectum	0-IIa+IIc	within a polyp surrounding the tumor
3.	Yasunaga, 1992[6]	76	M	Ascending	0-IIa+IIc	submucosa
4.	Imamura, 1993[7]	50	M	Rectosigmoid	unknown	not stated
5.	Suzuki, 1993[8]	50	F	Rectum	type 2	submucosa regional lymphnodes
6.	Abe, 1994[9]	31	F	Sigmoid	type 2	not stated
7.	Hideshima, 1994[10]	59	M	Rectum	0-IIa+IIc	submucosa
8.	Hideshima, 1994[11]	68	M	Rectum	type 3	not stated
9.	Kurosaki, 1996[12]	75	M	Rectum	type 2 (carcinoid)	submucosa
10.	Okamoto, 1996[13]	77	M	Sigmoid	type 1	subserosa regional lymphnodes

Japan,[16] accurate numbers of patients with chronic schistosomiasis are difficult to obtain because of the lack of physician's awareness and a low index of suspicion. Regrettably, we did not find this patient's colonic tumor until it had reached an advanced stage.

Several reports indicate that patients with schistosomiasis have significantly higher colorectal cancer mortality rate, onset at an early stage, and more aggressive potentiality than non-parasited individuals.[1] Long-term follow-up of individuals treated for schistosomiasis will be helpful in resolving issues relating to oncogenesis and improving the prognosis for those who develop cancer.

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