Vaterian Cancer in Siblings

JOHN C. AUSTIN, M.D., CLAUADE H. ORGAN, JR., M.D., F.A.C.S., G. RAINIE WILLIAMS, M.D., F.A.C.S.,
and JAN V. PITHA, M.D., Ph.D.

From the Departments of Surgery and Pathology,
University of Oklahoma Health Sciences Center,
Oklahoma City, Oklahoma

The simultaneous occurrence of Vaterian carcinoma in two siblings suggests a genetic influence in their pathogenesis. Their classic clinical presentation of obstructive jaundice and weight loss required pancreaticoduodenectomy for this neoplasm. Pedigree analysis revealed a third sibling who died from an unresectable peripancreatic malignancy. Neither of the probands exhibited, as late as the seventh decade, evidence compatible with a diagnosis of familial polyposis coli or Gardner's syndrome. Flow cytometry studies revealed an aneuploid distribution in one tumor and tetraploid in the other. The rarity of this neoplasm, in the absence of contributing epidemiologic factors, suggests that this is a pleiotropic manifestation of a cancer-prone genotype.

CARCINOMA of the ampulla of Vater, a rare tumor of the duodenum, constitutes 0.01% of solid tumor cases and is found in 0.2% of postmortem examinations.1 The overwhelming number of malignant ampullomas appear sporadically in the population and are considered to be multifactorial in origin and nonheritable. A previous report presented to this association in 19762 discussed the association of peripancreatic malignancies, Gardner's syndrome (GS), and familial polyposis coli (FPC). The simultaneous occurrence of this rare duodenal neoplasm in sibling males suggests a genetic influence on pathogenesis.

Case Reports

Case 1. A 66-year-old man presented to the hospital with a 3-week history of painless jaundice, dark urine, and a 6-month weight loss of 15 lb. He denied any previous history of hepatitis or pancreatitis, although a single-unit blood transfusion was received during an uncomplicated cholecystectomy 15 years prior to admission for cholelithiasis.

Presented at the 100th Anniversary Meeting of the Southern Surgical Association, Hot Springs, Virginia, December 6–9, 1987.
Reprint requests and correspondence: Claude H. Organ, Jr., M.D., University of Oklahoma Health Sciences Center, Department of Surgery, P.O. Box 26307, Oklahoma City, OK 73126.

Past medical history was unremarkable except for moderate controlled hypertension. Medications included clonidine and a tricyclic antidepressant. Physical examination demonstrated a deeply jaundiced, emaciated man. Except for an enlarged liver, abdominal examination was unremarkable for tenderness or palpable masses.

Abnormal laboratory data included a total bilirubin of 15.5 mg/dL, alkaline phosphatase of 575 U/L, and an SGOT of 213 U/L (Table 1). Computed axial tomography (CAT) of the abdomen revealed a cystic mass in the head of the pancreas, dilated intrahepatic and extrahepatic bile ducts, and no significant periaortic lymph node enlargement (Fig. 1). Percutaneous transhepatic cholangiography confirmed the presence of gallstones plus intrahepatic and extrahepatic biliary duct dilation secondary to a distal common duct obstruction. Diffuse enlargement of the pancreatic duct was demonstrated on endoscopic retrograde cholangiopancreatography (Fig. 1). Biopsy of a friable mass at the ampulla of Vater proved to be adenocarcinoma on frozen section.

At laparotomy a small mass was present in the head of the pancreas with no evidence of hepatic or lymph node metastases. Pancreaticoduodenectomy was performed uneventfully. The presence of a 2-cm ampullary adenocarcinoma was confirmed on microscopic examination; ten identifiable lymph nodes were free of tumor (Fig. 2). The patient was discharged on the 16th postoperative day following an uncomplicated course. Subsequent colonoscopy and barium enema, performed because of concern that the lesion might be associated with FPC, were both within normal limits with no evidence of gastrointestinal polyps. At 16 months there were no signs or symptoms of recurrent disease with normal nutrition. The patient expired 30 months after the operation. Postmortem examination was not obtained.

Case 2. A 64-year-old brother of Case 1 had always been in good health. Two weeks after his brother's operation he was admitted with similar symptoms, i.e., a 2-month history of painless jaundice, dark urine, and a 22-lb weight loss. Hepatitis profile was HAV antibody and HB core antibody positive; HB surface antigen and IgM were negative (Table 1). There had been no previous serious illnesses, operations, or hospitalizations. On physical examination he was emaciated and icteric. Abdominal examination revealed an enlarged liver 12–13 cm wide at the midclavicular line. Abnormal laboratory values included a total bilirubin of 9.4 mg/dL, alkaline phosphatase of 410 U/L, SGOT of 239 U/L, and guaiac-positive stools (Table 1).
Ultrasonography of the pancreas and biliary tree demonstrated dilated intrahepatic and extrahepatic biliary ducts without evidence of choledolithiasis. An abdominal CT scan revealed no evidence of a pancreatic mass or perisaoic-pericaval lymphadenopathy. On ERCP a friable fungating mass was observed at the ampulla of Vater and a dilated pancreatic duct was demonstrated (Fig. 3). Biopsy of the mass was compatible on light microscopy with a diagnosis of an infiltrating, moderately well-differentiated Vaterian adenocarcinoma (Fig. 4).

Following 1 week of hyperalimentation a successful pancreaticoduodenectomy was performed. Histologic examination of the specimen revealed a 4-cm malignant ampullary adenocarcinoma; two of seven lymph nodes were positive for tumor. The immediate postoperative period was complicated by bilateral lower lobe pneumonia. The patient was discharged 1 month following the procedure. Case 2 was free from disease for approximately 1 year after operation when CAT scan confirmed the presence of hepatic and regional metastases. A moderate objective response was observed with 5-fluorouracil (5-FU) therapy. The patient died 18 months after surgery with extensive recurrent intra-abdominal disease. Postmortem examination was not obtained.

Case 2, whose tumor was large and infiltrating with metastatic lymph nodes, exhibited biologic aggressiveness. In comparison the tumor in Case 1 was small without lymph node involvement and was less aggressive.

Chromosome analysis of both patients demonstrated no morphologic abnormality in either patient with conventional G-banding, C-banding, and karyotypes. HLA typing failed to reveal any significant correlation between these siblings: HLA typing on Case 1 was A11, A33, B8, DR1, DR7; while Case 2 was A2, A3, B44, D35, DR1, and DR5 (Table 2).

Flow cytometry studies were performed to determine ploidy distribution in deparaffinized tissue specimens. Flow cytometric DNA analysis of cell nuclei stained with propidium iodide revealed two normal DNA distributions including normal percentages of cells in both G0-G1 and G2-M phases. Two other DNA distributions were identified as abnormal: one exhibited a hypodiploid distribution of cells.
included in the G0–G1 phase and the other exhibited a tetraploid distribution of cells. Peak channels for the cells in the DNA distribution are as follows: the normal DNA distributions were from normal tissue; the abnormal DNA distributions (tetraploidy) represented malignant tissue.

An outline of this kindred presented in Figure 5 reveals a younger sister who had an exploratory laparotomy at another hospital in 1979. The operative findings were compatible with a periampullary neoplasm, although it was not possible to determine the specific site of origin. Intraoperative biopsy of a liver nodule confirmed the presence of metastatic cancer. Investigation of other available siblings revealed evidence of an occasional gastrointestinal polyp but no evidence of FPC.

**Discussion**

The presence of ampullary carcinoma in two male siblings simultaneously presenting within 2 weeks of each other in their seventh decade, and the identification of a third sibling deceased from a periampullary malignancy, suggests a phenotypic expression of a deleterious gene and not a chance occurrence. The odds against two siblings out of 11 developing pancreatic cancer in the same year, in the absence of a genetic factor, is 100,000,000:1. Cancer of the ampulla of Vater is even more rare, and the odds are even greater against two siblings developing the disease. Previous authors have associated periampullary cancer with FPC and GS.

Vaterian cancer, like other malignancies with limited numbers available for study, has not undergone careful epidemiologic review. The influence of genetics on this neoplasm has been given little attention with regard to its pathogenesis. Geneticists understandably have concentrated their studies on unifactorial disorders that occur more frequently in the population. This neoplasm, in the absence of an identifiable single-gene determined etiology, should be considered multifactorial in origin. Such multifactorial disorders are presumed to result largely from the additive effect of a number of factors, some genetic and others environmental. A variety of aneuploid states, single-gene disorders, and other...
TABLE 2. HLA Typing

<table>
<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>A11</td>
<td>A2</td>
</tr>
<tr>
<td>A33</td>
<td>A3</td>
</tr>
<tr>
<td>B8</td>
<td>B44</td>
</tr>
<tr>
<td>DR1</td>
<td>D35</td>
</tr>
<tr>
<td>DR7</td>
<td>DR1</td>
</tr>
<tr>
<td></td>
<td>DR5</td>
</tr>
</tbody>
</table>

polygenic conditions may predispose to malignancy, although the exact molecular mechanisms are rarely clear. The complexity and importance of host factors in such tumors become increasingly important and are very difficult to discern.

The most attractive hypothesis for the simultaneous occurrence of this unusual phenomenon is that it is a variant of FPC or GS. It is difficult for the surgeon and pathologist to differentiate between carcinoma arising from the mucosa of the second part of the duodenum, the ampulla of Vater, and the intramural segments of the common bile and pancreatic ducts. Periampullary carcinoma has been described in approximately 30 patients with GS and is recognized as more than a chance occurrence in this syndrome.\(^5\) The wide spectrum of extracolonic manifestations identified with GS reflects the variability of gene penetrance. Whether or not a familial occurrence can be implicated in periampullary carcinoma without colonic polyoid disease is conjectural. Neither of these siblings demonstrated colonic or other manifestations of GS as evidenced by normal physical examination, barium enema, and skeletal survey.

The familial aggregation of site-specific neoplasms should be confirmed by pedigree analyses. Of the 11 siblings in this kindred, the two probands and the younger sister discussed in this report died of ampullary or periampullary cancer. Four of the remaining eight have expired of cirrhosis, diphtheria, blood poisoning, and a cerebrovascular accident. Only one of the four living siblings has exhibited interest and agreed to a screening and follow-up studies. One proband worked in a flour mill and the other was a crane operator. No significant environmental or unusual lifestyle circumstances were discoverable from interviews with multiple family members; hence this unique occurrence cannot be accounted for by any known environmental factors.

In the cancer family syndrome a pattern of malignancies emerges, although every individual does not necessarily have the same neoplasm. Familial tumors share several cardinal features: (1) they tend to occur at an earlier age, often 12–15 years before sporadic cases appear; (2) there is an increased incidence of synchronous and metachronous lesions; (3) they may be multicentric and/or bilateral where paired organs exist; (4) there is an excess of 25% of the family members affected who are in direct lineal descent from the proband; and (5) the cancer predisposition in these families behaves as an autosomal dominant trait with a 60% or more penetrance.

There are several possible explanations for the phenotypic expression of Vaterian cancer in these male siblings. The tumors in this family may be due to: (1) chance alone, although this is unlikely; (2) the late penetrance of a GS genotype; (3) tumor heterogeneity caused by a different allele at the same locus; or (4) a pleiotropic manifestation of a cancer-prone genotype being expressed as a result of environmental changes.\(^6\)

In 1935 Cabot\(^3\) described a 36-year-old man (Case No. 21061 from the Massachusetts General Hospital) with weakness, diarrhea, ankle edema, and jaundice.

---

**Fig. 5.** An outline of kindred for Cases 1 and 2.
who had several manifestations of GS (Table 3). At abdominal exploration for obstructive jaundice he was found to have an ampullary cancer and multiple intestinal polyps. No segment of the gastrointestinal tract greater than 3 cm in length was uninvolved with polyps. Bony exostosis existed in this deformed male with a prior history of having several hard masses removed from the skull, ribs, and mandible. He also had a previously resected fibrosarcoma. His grandmother died of carcinoma (site unknown) and his mother of rectal carcinoma at age 34. Multiple members of the family (mostly females) and their offspring for three previous generations were afflicted with similar bony growths.

Macdonald et al.⁴ in 1967 reported two cases associating GS with FPC and periampullary malignancies. Both patients had clinical evidence of FPC and GS. However, one of the periampullary malignancies was located in the head of the pancreas and the other in the ampulla of Vater. One patient had an associated renal adenoma and the other a papillary duodenal adenoma at some distance from the ampulla.

Watne et al.⁵ in 1975 reported 11 families with GS involving 280 patients. Two associated cases of Vaterian cancer, one malignancy in the liver and one in the pancreas, were present in these cohorts. However, in 41 cases intestinal cancer developed, often appearing at an earlier age for each successive generation.

Nance and Jones⁶ in 1977 reported three females with carcinoma of the ampulla of Vater, all of whom had FPC. Two of their cases were from the same kindred. All of their patients fulfilled the criteria of Morson and Bussey⁷ for the diagnosis of FPC; however, none expressed the classic features of GS as they are currently known. They postulated that GS should be viewed as an extracolonic variant of FPC and not as a separate disease process. They also concluded that the FPC patient having extracolonic lesions was an example of GS.

Lynch et al.⁸ in 1985 reported a family study of pancreatic carcinoma and hereditary nonpolyposis colorectal cancer. This kindred exhibited vertical transmission of cancer through five generations with a high frequency of associated hereditary nonpolyposis colorectal cancer. They appropriately suggested a need for more biomarker and pedigree studies with better documentation of cancer at all sites.

Several factors mitigate against the diagnosis of GS in the cohort group: no polyps; the absence of extracolonic manifestations of FPC; the absence of metachronous or synchronous lesions; and no instances in this family up to the present time of osteomas, soft tissue tumors, dental anomalies, thyroid cancer, ovarian or carcinoid tumors, lymphoma, fibrosarcoma, brain tumor, skin pigmentation, or FPC.⁹,10

In tumors that are heritable, two mutation events are required, the initial one being germinal and the second somatic.¹¹ Nonfamilial tumors tend to be unifocal and appear at a later age because two distinct somatic events would be required for tumor development. Implicit in this two-hit hypothesis is the assumption that carcinogenesis is related to discrete random changes occurring at a constant average rate. The occurrence of these ampullomas in the seventh decade in male siblings would presently be better placed in the nonfamilial category until such time as there is greater penetrance and expressivity to suggest a diagnosis of GS or FPC.

Of the 12 cases reviewed in this communication with the association of Vaterian carcinoma, FPC, and GS, three of the tumors were periampullary (25%), not specifically Vaterian in origin (Table 4). Confirmed FPC was reported in nine cases (75%) and in a single case of hereditary nonpolyposis colorectal cancer. Six of the 12 cases (50%) met reasonable criteria for a diagnosis of GS. If the assumptions of Jones and Nance¹² are valid, these numbers would then increase to nine of 12 (75%). No specific trend in morphologic categorization using the criteria outlined by Blumgart and Kennedy¹¹ could be ascertained. The nine ampullomas, according to this categorization would be as follows: Type I, three; Type II, two; and Type III, four. HLA typing when compared with matched controls demonstrated no difference.

| Table 4. Association of FPC, GS, and Vaterian Carcinoma in 12 Patients |
|-----------------------------|-----|-----|-----|-----|
| PH  | AV  | Yes | No  |
| Site | 25% | 75% | —   | —   |
| FPC | —   | —   | 75% | 25% |
| GS  | —   | —   | 50% | 50% |

PH = pancreatic head.
Genetic counseling and screening for these families is important to reduce their obvious hidden family anxiety. In the absence of a specific biomarker(s), the accuracy of the pedigree analysis becomes increasingly important requiring histologic confirmation of the disease(s) existing in this kindred. Where biochemical markers exist they must be obtained and repeated as part of the follow-up process. Syndromes such as FPC and GS seldom present all of their classic features when initially discovered. The unfolding and phenotypic expressions among these cohorts require close monitoring. The importance of this familial or hereditary pattern of tumor distribution is emphasized by the recent report of their improved survival.12

References

Discussion

Dr. Alvin L. Watne (Peoria, Illinois): First, I want to extend my welcome to Claude and Betty on their membership in the Association. I want to congratulate the authors on their work on what I think is a very important observation. Opportunity comes to those who have an alert mind and make a critical observation, and I want to thank them for sharing their manuscript with me. I took the liberty to bring along a few slides. I've assured Claude that I would not have a 29-page discussion.

(Slide) The question came up about the relation to Gardner's Syndrome. Both Gardner himself and our group now feel that Gardner's Syndrome is probably the ultimate manifestation of the inherited characteristic. As you can see, 60% had soft tissue tumors, 30% had bony tumors, and two-thirds of them showed polypos. So we had patients with soft tissue tumors and no polypos. We had patients with polypos and no soft tissue tumors.

(Slide) Here is this broad group of manifestation of tumors that show up in this syndrome that Dr. Organ referred to, and you will notice that two of our patients had carcinoma of ampulla of Vater. Dr. Julian Ambrose took a look at this group of patients, and he said, “It looks like you were feeding them a carcinogen.” The patients with carcinoma of the ampulla of Vater had no other manifestations of Gardner's Syndrome. However, relatives in their families did show the syndrome.

(Slide) One of these patients was particularly interesting. This 18-year-old girl entered our hospital in 1973 with (by history and physical examination) an obvious carcinoma of the ampulla of Vater. Her colon had been removed for polypos 2 years previously. She underwent a decompression cholecystojejunostomy, and, at that time, we could palpate a small tumor at the ligament of Treitz. After about an 8-week period, she then underwent a pancreateco-duodenectomy, including the gallbladder and the cholecystojejunostomy, and during that interval of about two months, she had developed another adenomatous polypl right at the cholecystojejunostomy.

(Slide) In 1978, this girl developed a cystadenocarcinoma of the ovary, and in 1982, we removed her rectal segment for three carcinomas that had developed despite repeated proctoscopic examination; so this girl manifested three different malignant neoplasms in her life.

(Slide) That brought us to study any associated inherited characteristics, and in our patients we found that there was a marked increase in the cholesterol fraction and the primary bile acid fraction in the fetal steroids of patients with polyposis coli or Gardner's Syndrome.

We have also recently seen that there is an increase in the glycolyl transferase activity and a decrease in the glycolycolin formed in the colonic mucosal cell wall of these patients.

(Slide) One last point that will lead to a question: These patients have been shown by Utsumonoiya to develop gastric and duodenal polyps. So I will now ask some questions of Dr. Organ, if I might.

The first question would be: Have you noticed any other physiological or biochemical changes such as alterations in fetal steroids, bile salts and increased or decreased incidence of cholelithiasis. Have you extended your study of your patients to the cousins? You must extend that family group that you showed us because the manifestations may appear in other family members. The patients may have expired before the manifestations appeared, and the trait will show up in the next generation. Have you any data regarding the incidence of polypos of the upper gastrointestinal tract in these patients, and what would be your approach to an adenomatous polypl of the upper gastrointestinal tract in these patients?

Dr. F. Carter Nance (Livingston, New Jersey): I enjoyed Dr. Organ's and Dr. Watne's paper and would like to give one of my own. (Slide) Dr. Organ was kind enough to mention my study. We found a similar problem and reviewed 19 reported cases of periampullary carcinoma in patients with Gardner's Syndrome. We did stretch the diagnosis of Gardner's Syndrome, feeling that any manifestation of the familial polyposis syndrome associated with extracolonic findings should be grouped in that category.

I think the striking thing for us was that most of these patients were presented at an early age with the periampullary carcinoma. (Slide) And another striking aspect was that the type of periampullary malignancy was ampulla of Vater in most of them—although duodenal pancreatic and undetermined.

As Dr. Watne mentioned, (Slide) our recommendations on the basis of our findings, at least, for the patients who have the marker of familial polyposis.
familial polyposis are that there be routine surveillance not only of the lower gastrointestinal tract (if any colon is left), but routine surveillance of the upper gastrointestinal tract, endoscopic biopsy removal of all duodenal and gastric polyps and surgical removal of recurrent or malignant polyps.

Unfortunately, in this group of patients that Dr. Organ has presented, there isn’t a convenient marker of familial polyposis, and I guess that really raises my biggest question. Has he identified anything in these families that will allow us to identify the cohort and to do some sort of reasonable surveillance in this group of patients?

It is a beautifully studied family, but I would hope that he can extend his familial study, as Dr. Watne suggested, to identify any further members of the cohort and to identify any markers that we could use for rationale surveillance.

Dr. John C. McDonald (Shreveport, Louisiana): I was honored that Dr. Organ would ask me to discuss his first presentation as a member of this society.

This paper should be considered in the context of a series of publications by Dr. Organ on familial cancer, a subject in which he has had an abiding interest.

In the apparent effort to find some genetic marker to relate to these patients, he studied the HLA locus and found no relationship, and it is that point that I would like to discuss.

Some 20 years ago a small paper was published which seemed to show a relationship between the H2 phenotype and murine leukemia. Shortly thereafter, immune response genes were discovered and related to the major histocompatibility locus. These two observations set in motion an avalanche of studies all designed to relate some disease state to the HLA phenotype or genotype.

Some 20 years later there are at least four or five dozen such conditions well established statistically. These disease processes generally fall into two general categories. One is a series of arthropathies of which Reiter’s Syndrome is a prototype, and the other is a large variety of diseases that seem to be related to autoimmunity.

It is ironic that even though the original observation was related to a malignant condition, after 20 years there is not a single human malignancy that appears to have been reliably related to the HLA locus. So while one intuitively believes that there must be a genetic marker or genetic information that is related to these familial cancer syndromes, it appears not to be HLA locus.

Dr. Claude H. Organ, Jr. (Closing discussion): I wish to thank Dr. Watne and Dr. McDonald for their contribution; we relied on their work to point us in the right direction. Research gives and research takes away. We have been the beneficiaries since World War II of superb research in the United States and worldwide; and just as research takes procedures away from us, it affords us new opportunities.

Genetics offers that opportunity for us.

It is said that the clinician or the clinical investigator is a vanishing breed, and that the basic scientists are in one part of the university and the clinicians in another. It behooves us as clinicians to become involved with these studies. I am not a geneticist, but I realize the benefits that can accrue from this. These pedigree analyses are very difficult to formulate. Again I thank Dr. Austin, one of our very talented residents who has narrowed his interest and talents down to thoracic surgery for dealing with a very difficult family that is fearful of being called a cancer family. Usually there is a family historian to be dealt with whose confidence must be gained, who has a family bible or can give you much of this information.

Dr. Watne, in the large series from Omaha that is masterminded by Dr. Henry Lynch, (glycoproteins or fecal steroids were not dealt with. At the Familial Institute they have had as one of their main areas of concentration the development of pedigree analysis. These are very hard to compile because once you get beyond first-degree relatives in our mobile society, it is difficult to obtain information from second-degree relatives.

These pedigrees have been studied with a number of enzymes and biochemical markers, recently including alpha-fucosidase.

The studies on twins with cancer have been remarkably unproductive. This genotype will be carried by a male and be phenotypically expressed in the next generation in the other sex.

This is a difficult family. We have had a difficult time getting them in, and we don’t know what the G.I. tract of many of them really looks like. If polyps are high in the G.I. tract, they should be scoped often and as many of them excised endoscopically as possible. There tends to be an aboral increase in the incidence of malignancy or the propensity toward malignancy, that is, it would be lower in the stomach than in the colon. Therefore, endoscopic removal of these and endoscopic review of these on a periodic basis, alternating with barium swallow and/or enema, would be indicated.

It has certainly raised the possibility of gastric mucosectomy, a procedure that would be a little more vascular than rectal mucosectomy if you are operating on the same type of stomachs that I am.