J Clin Gastroenterol 1997;24(4):276–279.

Peritoneal Mesothelioma in Recurrent Familial Peritonitis

Nicola Gentiloni, M.D., Stefania Febbraro, M.D., Carlo Barone, M.D., Gianfranco Lemmo, M.D., Giovanni Neri, M.D., Gianfranco Zannoni, M.D., Arnaldo Capelli, M.D., and Giovanni Gasbarrini, M.D.

A 39-year-old man had a 2-year history of fatigue, weight loss, drug-resistant ascites, and decreased intestinal motility. During adolescence he began to suffer frequent episodes of acute benign peritonitis that spontaneously subsided at age 35. The fact that his younger brother was taking colchicine for the same symptoms led us to diagnose familial Mediterranean fever (FMF). The medical workup revealed uniform thickening of the intestinal wall with no signs of amyloidosis. Exploratory laparotomy revealed diffuse peritoneal mesothelioma that proved to be unresponsive to chemotherapy. There was no history of asbestos exposure. It is probable that the chronic peritoneal inflammation was responsible for the development of this tumor, although in almost all cases of FMF this phenomenon causes only limited peritoneal fibrosis or, less commonly, encapsulating peritonitis. A computerized search of the literature indicates that this is the second report of peritoneal mesothelioma associated with FMF.

Key Words: Familial Mediterranean fever—Malignant mesothelioma—Colchicine.

Mesothelioma is a primary tumor arising in the pleura or, less commonly, the peritoneum and pericardium. Localized forms are usually benign, whereas diffuse involvement generally indicates malignancy. The most important cause of these tumors is asbestos exposure, and the incidence among exposed populations ranges from 13% to 100% (1). Exposure to other fibers, mineral dust, various chemicals, and ionizing radiation as well as chronic serosal inflammation are also considered to increase the risk for these tumors (2). The possibility that hereditary factors are involved in the development of mesothelioma was first raised in 1985, when Lynch et al. (3) described 11 patients with mesothelioma in four unrelated families. However, 10 of these patients had histories of asbestos exposure.

We describe a 39-year-old man in whom a malignant peritoneal mesothelioma developed after a 20-year history of recurrent peritonitis related to familial Mediterranean fever (FMF).

PATIENT REPORT

In January 1994, a 39-year-old Italian man of non-Jewish ancestry was admitted to our medical center with a 2-year history of decreased appetite, progressive weight loss, occasional diarrhea, fatigue, low-grade fever, and drug-resistant ascites. At the age of 16 years, the patient had begun to suffer frequent, self-limiting bouts of acute abdominal pain associated with fever, bowel distention, obstipation, and failure to pass flatus. Between attacks, he was completely asymptomatic. These episodes, which generally lasted 24 to 72 hours, continued to occur approximately once a month until age 35, when they subsided spontaneously. At age 37, the symptoms that brought him to our hospital began to develop.

The patient's younger brother (age 29 years in 1994) had a history of nontuberculous pleural effusion at the age of 20 years. Since then he had experienced the same type of recurrent abdominal pain with decreased intestinal motility. He had already undergone two laparotomies that had no effect on his symptoms. In 1992 he began daily treatment with colchicine, and since then his acute attacks had been decreasing in both frequency and intensity.

On physical examination, the patient appeared cachectic with marked abdominal distention resulting from ascites without collateral superficial veins. The liver and spleen were not enlarged, and there were no palpable lymph nodes. The heart and lungs appeared normal.

Laboratory findings were as follows: total serum proteins, 5.6 g/dl; serum albumin, 2.8 g/dl; serum iron, 16 μg/dl; fibrinogen, 641 mg/dl; transferrin, 109 mg/dl; prothrombin time, 88%; hemoglobin, 9.7 g/dl; red blood cell count, 3,165,000/mm³; mean cor-

Received January 30, 1996. Revision sent March 19, 1996. Accepted January 27, 1997.

From the Institute of Internal Medicine and Geriatrics, Institute of Geriatric Surgery, Institute of Anatomy and Pathology, and Institute of Genetic Medicine, Catholic University of the Sacred Heart, Rome, Italy.

Address correspondence and reprint requests to Dr. Nicola Gentiloni, Policlinico A. Gemelli, Largo A. Gemelli, 8, 00168, Rome, Italy.

puscular volume, 83 femtoliter (fl); white blood cell count, 9,600/mm^3 (balanced leukocyte formula); total lymphocytes, 672; $CD4^+/CD8^+$, 0.8; human immunodeficiency virus, 1/2 negative; total urinary porphyrin, normal. A tuberculin skin test was negative, as was serology for anugliadin antibodies, endomysium antibodies, and antinuclear antibody. Circulating immune complexes were normal.

Paracentesis revealed exudative ascites consisting of sterile peritoneal fluid with polymorphic inflammatory cells and no neoplastic cells. Renal function was normal, and there was no albuminuria. The xylose and sorbitol breath tests were normal. The lactulose breath test suggested decreased small bowel motility with bacterial overgrowth. Stool cultures were negative.

A rectal biopsy was mildly positive for amyloid (Congo red). Histologic examination of multiple biopsies of the duodenal and jejunal mucosa revealed normal villous architecture with no signs of amyloid or pathologic cells. Results of colorectal biopsies and the percutaneous liver biopsy were negative.

On abdominal sonography, the liver, spleen, and stomach appeared normal, and there was no portal hypertension. The intestinal wall was mildly thickened. Computed tomography and magnetic resonance imaging confirmed the normal appearance of the liver and spleen. The thick ascitic fluid appeared to contain protein and cells. The intestinal mesenterium was evident, and the entire bowel wall was uniformly thickened without any evidence of localized masses or pathologic lymph nodes. On the small intestinal barium study, Kerckring's folds and intestinal lumen appeared normal, but intestinal motility was markedly decreased, and the barium reached the terminal ileum 4 hours after ingestion. Results of the barium enema were normal.

In light of the family history, it seemed fairly clear that the patient's attacks between the ages of 16 and 35 were a manifestation of FMF, but the cause of his more recent symptoms remained obscure. Exploratory laparotomy was performed to rule out the presence of intestinal amyloidosis.

Surgery revealed marked, diffuse thickening of the visceral and parietal peritoneum with cordlike structures (Fig. 1). Histologic examination of the latter demonstrated an epithelial neoplasm (Fig. 2) that was negative for periodic acid–Schiff/diastase. Immunohistochemical studies were negative for carcinoembryonic antigen and Leu M1 and positive for keratin and EMA. These findings, although not specific, were highly suggestive of mesothelioma.

The patient was started on doxorubicin and platinum but died 6 months later. At autopsy, the tumor was essentially unchanged. There were no signs of intra-abdominal organ infiltration or distant metastases.

FIG. 1. Laparotomy: diffuse and massive thickening of the peritoneum, which appears lardaceous with orange-peel surface. The peritoneum covers the intra-abdominal organs and fixes the intestine, as a rigid tangle, to the posterior wall of the abdomen. It forms cordlike structures all around the intestinal loops, the lateral wall of the abdomen, the liver, and the spleen.

DISCUSSION

Malabsorption resulting from celiac sprue or small bowel lymphoma with ascites was excluded by the normal mucosal biopsies and serologic markers. The patient's history and that of his brother were highly indicative of FMF, and although there was no sign of amyloid material in the mucosal biopsies from the duodenum or jejunum, we initially suspected that the diffuse, uniform thickening of the small bowel wall and markedly reduced motility might be due to amyloid deposition in the external muscle layer.

The surgical biopsies instead revealed a tubopapillary epithelial neoplasm, with immunohistochemical features of mesothelioma, that involved both the visceral and parietal peritoneum. The extent of the abdominal involvement and the clinical evolution of the disease were more indicative of malignancy than were the histologic findings.

In the presence of asbestos exposure, the symptoms this man had been experiencing for the past 2 years (cachexia, intractable ascites, reduced intestinal motility), although nonspecific, would have been suggestive of peritoneal mesothelioma (4). However, neither the patient nor his brother had been exposed to this substance or any of the other substances implicated in the appearance of this tumor. The only plausible explanation for the tumor was the patient's long history of "benign peritonitis," which was diagnosed as FMF.

FMF is a genetic disorder of unknown cause that is restricted to certain Mediterranean populations, particu-

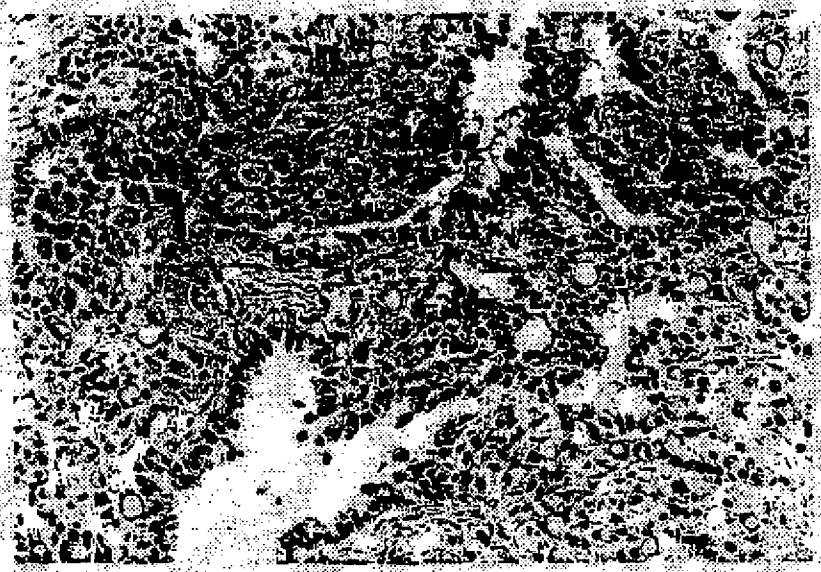

FIG. 2. Histologic evaluation shows diffuse tubopapillary neoplasm of the epithelial type.

larly the Arabs of the Middle East, Anatolian Turks, and Armenians. In Jewish ethnic groups, the frequency of heterozygous carriers also appears to be quite high, ranging from approximately 3% in the Ashkenazic subgroup to 20% among the Jews of Libya (5). Rare cases have also been reported in non-Jewish Italians (6).

In 1961, Heller et al. (7) suggested that FMF was inherited as a single autosomal recessive trait. A mutant FMF gene with pleiotropic effects (known as the MEF gene) has been mapped on the short arm of chromosome 16 (8). Observations suggest that there may also be a second gene that causes a milder form of the disease with autosomal dominant characteristics (9).

The clinical presentation is usually a variable combination of two different phenotypic expressions. Type I FMF is primarily characterized by recurrent, self-limiting attacks of serosal inflammation involving the peritoneum, pleura, and synovia. Two thirds of all patients with this type of disease undergo unnecessary laparotomy for "acute abdomen," and surgery is generally well tolerated but ineffective. In type II FMF, the major feature is insidious systemic deposition of AA-amyloid that is particularly marked in the kidneys. In 90% of these patients, renal failure develops before age 40 years. The amyloidosis generally appears to be caused by the chronic inflammation, although in many cases it precedes the abdominal symptoms and may remain the only manifestation of the disease. Forms of FMF with persistent fever as the only symptom and no family history have also been described (10), and diagnosis is difficult in these cases.

For the moment, there is no specific procedure for the diagnosis of FMF. Positive responses in the metaraminol provocation test and elevated plasma levels of dopamine B-hydroxylase were considered highly specific for FMF when the disease was thought to be caused by an inborn error of catecholamine metabolism, but this hypothesis has now been abandoned. Israeli investigators have demonstrated a striking reduction in the in vitro production of inducible tumor necrosis factor by peripheral-blood mononuclear cells during acute FMF attacks and a fivefold increase over normal in serum tumor necrosis factor levels during asymptomatic intervals (11). These findings suggest that tumor necrosis factor may play a role in the pathogenesis of the disease and raise the possibility of a specific diagnostic test based on serum levels. Systemic perivascular AA-amyloid infiltration can be demonstrated in bone marrow biopsies using an immunoperoxidase stain and monoclonal antibody (12).

In the early 1970s, two double-blind, placebo-controlled trials showed that colchicine could prevent the acute attacks in FMF and reduce the incidence of renal amyloidosis by approximately two thirds when administered prophylactically (13,14). The drug has also been shown to reverse FMF-related nephrotic syndrome (15) and to prevent the recurrence of amyloid deposition after renal transplantation (16). All of the symptoms presented by our patient and his brother were typical of type I FMF, which appears to be more common among Italians than type II (unpublished observations), and there was no evidence of renal or intestinal amyloidosis in either case. In the absence of previous exposure to asbestos or other known risk factors, it seems probable that the malignant peritoneal mesothelioma was the result of chronic irritation caused by recurrent peritoneal inflammation. A case of malignant peritoneal mesothelioma was described by Riddell et al. in a patient with a 12-year history of recurrent diverticulitis, and chronic inflammation was suspected of contributing to the development of the tumor (17). However, the long-term effects of peritoneal

involvement in FMF are generally limited to localized fibrosis or encapsulating peritonitis (18). Malignant outcomes are rare, and there has been only one other report thus far of mesothelioma associated with FMF (19). The diffuse abdominal involvement in the present case suggests a polyclonal origin, and the long latency is consistent with the slow growth of this tumor.

Several chromosomal deletions have been found in patients with malignant mesothelioma, including some involving chromosome 16 where the MEF gene is located (20). Although there are no data to support this hypothesis, it is possible that the MEF also functioned as an oncogenic suppressor gene and that a subsequent mutation might have lead to the development of the mesothelioma.

Shortly after the patient's death, his brother underwent surgery for repair of a ventral hernia that had developed after a previous laparotomy. Careful exploration of the abdomen did not reveal any sign of mesothelioma. The absence of malignancy in this case is not surprising given the pleiotropic nature of the MEF gene, but it might also be a reflection of the attenuation of the inflammatory process achieved with colchicine. Nonetheless, the possibility that peritoneal mesothelioma will eventually develop in the younger brother, who is currently only 32 years old, cannot be ruled out, and he is currently being monitored by our staff.

Acknowledgment: We are grateful to Miss Marian Kent for her editorial assistance in preparing this article.

REFERENCES

1. Hammar SP, Bolen JW. Pleural neoplasm. In: Dail DH, Hammar SP, eds. *Pulmonary pathology*. New York: Springer-Verlag, 1988; 973–1028.
2. Riddel RH, Goodpasture MJ, Moossa AR. Peritoneal malignant mesothelioma in a patient with recurrent peritonitis. *Cancer* 1981;48:134.
3. Lynch HT, Kaur D, Markvicka SE. Familial mesothelioma: review and family study. *Cancer Genet Cytogenet* 1985;56:25–35.
4. Van Gelder T, Hoogsteden HC, Versnel MA, et al. Malignant peritoneal mesothelioma: a series of 19 cases. *Digestion* 1989; 43:222–7.
5. Daniels M, Shohat T, Brenner-Ullman A, Shohat M. Familial Mediterranean fever: high gene frequency among the non-Ashkenazic and Ashkenazic Jewish populations in Israel. *Am J Med Genet* 1995;55:311–4.
6. Chiloyi F, Dobrilla G. Familial Mediterranean fever: first report from Italy. *Ital J Gastroenterol* 1985;17:275–7.
7. Heller H, Sohar E, Gafni J, Heller J. Amyloidosis in familial Mediterranean fever. *Arch Intern Med* 1961;107:539–45.
8. Pras E, Aksentijevich I, Gruberg L, et al. Mapping of a gene causing familial Mediterranean fever to the short arm of chromosome 16. *N Engl J Med* 1992;23:1509–13.
9. Yuval Y, Hemo-Zisser M, Zemer D, et al. Dominant inheritance in two families with familial Mediterranean fever (FMF). *Am J Med Genet* 1995;57:455–7.
10. Cherem JH, Andrade SI, Lifshitz A, Nellan H. Persistent fever as the only symptom of familial Mediterranean fever. *Arch Intern Med* 1990;150:1347.
11. Schanmer A, Gurevitz A, Zemer D, Hahn T. Induced TNF production in vitro as a test for familial Mediterranean fever. *Q J Med* 1996;89:205–10.
12. Sungur C, Sungur A, Ruacan S, et al. Diagnostic value of bone marrow biopsy in patients with renal disease secondary to familial Mediterranean fever. *Kidney Int* 1993;44:834–86.
13. Dinarello CA, Wolff SM, Goldfinger SE, et al. Colchicine therapy for familial Mediterranean fever: a double-blind trial. *N Engl J Med* 1974;291:934–7.
14. Zemer D, Revach M, Pras M, et al. A controlled trial of colchicine in preventing attack of familial Mediterranean fever. *N Engl J Med* 1974;291:932–4.
15. Zemer D, Livneh A, Langevitz P. Reversal of the nephrotic syndrome by colchicine in amyloidosis of familial Mediterranean fever. *Ann Intern Med* 1992;116:426.
16. Livneh A, Zemer D, Siegal B, et al. Colchicine prevents kidney transplant amyloidosis in familial Mediterranean fever. *Nephron* 1992;60:418–22.
17. Aksentijevich I, Gruberg L, Pras E, et al. Evidence for linkage of the gene causing familial Mediterranean fever to chromosome 17q in non-Ashkenazi Jewish families; second locus or type I error? *Hum Genet* 1993;91:527–34.
18. Ciftici AO, Tanyel C, Buyukpamukcu N, Hicsonmez A. Adhesive small bowel obstruction caused by familial Mediterranean fever: the incidence and outcome. *J Pediatr Surg* 1995;30:577–9.
19. Banis YI, Artvinli M, Shain AA. Environmental mesothelioma in Turkey. *Ann NY Acad Sci* 1979;330:423–32.
20. Taguchi T, Jhanwar SC, Siegfried JM, et al. Recurrent deletions of specific chromosomal sites in 1p, 3p, 6q, and 9p in human malignant mesothelioma. *Cancer Res* 1993;53:4349–55.