Familial Mediterranean Fever and Peritoneal Malignant Mesothelioma: A Possible Association?

Tiberiu Hershcovici MD[1], Tova Chajek-Shaul MD[1], Tal Hasin MD[1], Suhail Aamar MD[1], Nurith Hiller MD[2], Diana Prus MD[3] and Hagit Peleg MD[1]

Departments of [1]Internal Medicine, [2]Radiology and [3]Pathology, Hadassah University Hospital (Mount Scopus), Jerusalem, Israel

Key words: familial Mediterranean fever, malignant mesothelioma, colchicines, asbestos

IMAJ 2006;8:509–511

For Editorial see page 501

Familial Mediterranean fever is a genetic disease with autosomal recessive inheritance and ethnic predilection. It is characterized by acute episodes of serosal membrane inflammation and an increased risk of renal amyloidosis. The disease and its complications are usually controlled with colchicine treatment. Malignant mesothelioma is a primary tumor of the pleura and less commonly of the peritoneum, pericardium and tunica vaginalis. Most cases are associated with asbestos exposure. Malignant mesothelioma in patients with FMF is very rare and its association with FMF is equivocal. We report two cases with both entities and discuss their association.

Patient Descriptions

Patient I

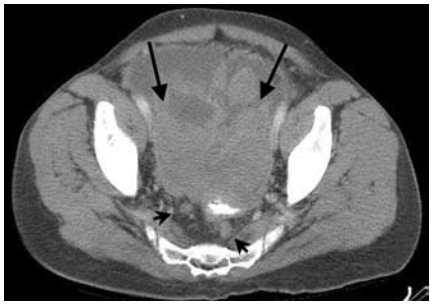
A 61 year old man of Jewish Moroccan ancestry was hospitalized because of progressive abdominal enlargement of 2 months duration. He suffered from attacks of fever and abdominal pain lasting 1–2 days and recurring once every few months from age 16 until the age of 20, when colchicine treatment was initiated leading to complete clinical remission. Genetic analysis revealed that the patient was homozygous for the M694V mutation in the *MEFV* gene. There was no history of asbestos exposure.

FMF = familial Mediterranean fever

Physical examination revealed marked ascites and bilateral leg edema. Paracentesis demonstrated a high protein high albumin gradient sterile peritoneal fluid with many polymorphonuclear leukocytes and mesothelial cells. Abdominal computed tomography showed ascitic fluid and large peritoneal implants in the subdiaphragmatic omental and mesenteric region. A solid pelvic mass was evident between the rectum and the bladder [Figure]. Laparoscopy showed diffuse thickening of the peritoneum. Histologic examination of the peritoneal biopsy material revealed epithelial-type malignant mesothelioma. Immunohistochemical stains were positive for keratin and calretinin (a specific stain for mesothelioma) and negative for BER-EP4 (a stain for carcinoma).

Patient 2

A 38 year old woman of Jewish Moroccan ancestry was admitted due to progressive abdominal enlargement of 2 weeks duration. There was no history of asbestos exposure. FMF was diagnosed clinically during her childhood, based on recurrent episodes of abdominal pain and arthritis. Colchicine treatment was prescribed, but not taken regularly. Genetic analysis revealed that the patient was homozygous for the M694V mutation in the *MEFV* gene. Family history was positive for FMF. Ten years prior to her admission, peritoneal adhesions were found and lysed during a laparotomy done as part of a workup for infertility.



CT of the pelvis demonstrates peritoneal fluid and a large solid mass at the recto-vesical pouch (arrows). Two round implants are seen posterior and lateral to the rectum (arrowheads)

Physical examination revealed an enlarged abdomen with shifting dullness. Paracentesis demonstrated a low protein high albumin gradient sterile fluid with many mesothelial cells. Abdominal CT showed a large amount of ascites with no peritoneal implants. Exploratory laparotomy showed turbid ascites fluid, lower abdominal peritoneal adhesions and multiple small peritoneal nodules. Cytology of the peritoneal fluid revealed atypical mesothelial cells strongly positive for calretinin and negative for MOC31 (which stains epithelial cells) and was consistent with mesothelioma. Biopsy showed foci of tumor consistent with epithelial mesothelioma. Tumor cells stained positively with keratin and calretinin and did not stain with BER-EP4.

Comment

Malignant mesothelioma is an aggressive tumor originating from the mesothelial cells lining the human body

cavities. Only 10–30% of these tumors are peritoneal mesotheliomas. Exposure to asbestos fibers is the etiology in most cases. Additional factors that possibly play a role in the pathogenesis of mesothelioma include exposure to SV40, other fibers, mineral dusts, various chemicals and ionizing radiation as well as genetic predisposition.

FMF is characterized by recurrent episodes of fever and serosal inflammation. Ninety-five percent of patients with FMF have abdominal serositis. The gene for FMF *(MEFV)* was mapped to the short arm of chromosome 16. Mutations and clinical disease are common in Turks, Armenians, Arabs and non-Ashkenazi* Jews. The mutation M694V that was found in both our patients is found in 63% of FMF patients of North African descent.

In FMF, mild and clinically undetectable ascites during attacks is common. The known long-term effects of peritoneal involvement are limited to localized fibrosis and encapsulating peritonitis. Recurrent peritoneal inflammation may predispose to malignant mesothelioma. Riddell et al. [1] report a patient who developed malignant peritoneal mesothelioma in a context of recurrent diverticulitis. The clinical picture and the lack of pathologic confirmation of diverticulitis on the surgical specimen may suggest that the patient suffered also from FMF.

There are only a few reports of patients with FMF and peritoneal mesothelioma. Chahinian and co-authors [2] reported a series of 69 cases of malignant mesothelioma, 12 of them localized to the peritoneum. One of the 12 patients had no known exposure to asbestos but had FMF with recurrent peritonitis. There are two other reports of FMF patients who developed malignant mesothelioma. Both had a long history of recurrent peritonitis and were never exposed to asbestos [3,4]. There is only one case report of pleural mesothelioma in a patient with FMF. This patient suffered from rheumatoid arthritis and late-onset FMF manifested by recurrent attacks of peritonitis and only rarely pleuritis [5].

Ashkenazi refers to Jews of East European origin

Is there an association between FMF and peritoneal mesothelioma or are the two cases we present mere coincidences? There are several arguments that support a true association between mesothelioma and FMF. First, the distribution of reported mesothelioma in FMF patients is different from mesothelioma in general. While most mesotheliomas are pleural, those in FMF patients have been predominantly peritoneal (three of four published cases), consistent with the fact that peritoneal inflammation is more common than pleural inflammation in FMF. Second, the coincidental occurrence of both diseases, though possible, is highly unlikely. Approximately 1:4.8 (21%) of Jews of North African descent are carriers of one of the three most common FMF mutations, i.e., 1% have the genetic makeup of FMF patients (though not all homozygotes have clinically active disease and some FMF patients have none or are heterozygous to known mutations). The age-standardized ratio of mesothelioma in Israel is less than 1:100,000 (data from the Israel Cancer Registry). The chance occurrence of FMF and mesothelioma is 1:10,000,000. Therefore, the diagnosis of two FMF patients with mesothelioma in one hospital with a catchment population of approximately 300,000 people is extremely unlikely to be coincidental. Lidar et al. [5] note that no case of mesothelioma was seen in 5000 cases of FMF in their clinic and therefore conclude that there is no association between the two illnesses. However, since the occurrence of peritoneal mesothelioma is very rare, even a 15-fold increase of incidence of mesothelioma in FMF (an increase similar to the well-established increased risk of colorectal cancer in ulcerative colitis) is possible without diagnosing a case of mesothelioma in 5000 patients. Third, there are various lines of evidence linking inflammation to cancer. In various malignancies the inflammatory process is a co-factor in carcinogenesis. Examples include the association of inflammatory bowel disease and colorectal cancer, hepatitis B and C virus infection and hepatocellular carcinoma, and Barrett's metaplasia and esophageal cancer. Although FMF is a paroxysmal illness there is evidence of an inflammatory activity between attacks. Inflammation can lead to tumorogenesis in a multi-stage fashion. Free radicals damage DNA and proteins. This damage against the background of increased proliferation can lead to mutations in various genes and result in dysplasia and invasiveness. Inflammatory cells can also produce growth factors, cytokines, etc. – all of which may contribute to the initiation and progression of cancer. For example, macrophage inhibitor factor is over-expressed in chronic inflammation and leads to reduced transcriptional activity of p53, thus leading to tumorogenesis. Cancer susceptibility and severity may be associated with functional polymorphisms of inflammatory cytokine genes. Examples include polymorphisms in the *IL-1* and *TNF* genes. Since pyrin (the *MEFV* product) may have a role in the cytokine pathway, a mutated pyrin might contribute to carcinogenesis.

Since FMF is not linked to an increase in the incidence of malignancies in Israel [5], it is unlikely that *MEFV* is a tumor suppressor. Conclusive evidence that FMF is a risk factor for peritoneal mesothelioma would require comparing the incidence of mesothelioma in FMF patients to its incidence in the general population. Because mesothelioma is so rare, one would need 16,000 FMF patients and 64,000 ethnically matched controls for 80% power to detect an odds ratio of 25 at a P value of 0.05. Since only approximately 10,000 patients with overt FMF are estimated to live in Israel, even if such a study was feasible it would lack sufficient power.

To summarize, we describe two patients of Jewish North African ancestry with FMF involving the peritoneum who presented with persistent ascites secondary to malignant mesothelioma. Both patients had recurrent peritoneal involvement during childhood, which abated during adulthood. Although causality cannot be proven, these cases suggest that local inflammation can lead to cancer at the same site. The association also raises the possibility that adherence to colchicine treatment may reduce the chance of mesothelioma secondary to reduction of inflammation.

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Correspondence: Dr. T. Hershcovici, Dept. of Medicine, Hadassah University Hospital, Mount Scopus P.O. Box 24035, Jerusalem 91240, Israel.
Phone: (972-2) 584-4520
Fax: (972-2) 581-2754
email: tiberiuh@md.huji.ac.il