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## Adenocarcinoid Tumor in a Patient with Familial Mediterranean Fever Operated for Perforated Appendicitis

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**Abstract:** In this study, 44 years old male suffering from abdominal pain and fever for a week admitted to emergency department. His family history revealed that younger sister has been diagnosed to have FMF and died from chronic renal failure 11 years ago. In chest x-ray, pneumoperitoneum was observed. The patient was operated for acute abdominal symptoms and found to have perforated appendicitis. Histopathologic examination was reported as adenocarcinoid tumor of the appendix with a tumor size of 3.5×2 cm. Patient was called for an interval right hemicolectomy. The genetic examination of the patient revealed M680I, M694V and E148G mutations. Familial Mediterranean Fever (FMF) is an important differential diagnosis of appendicitis. Patients should be evaluated meticulously in order not to be late for operation. Moreover, histopathological examinations of all specimens should be carefully made even of the negative appendectomy cases. A radical surgery could be dispensed if early diagnosis is achieved.

**Key words:** FMF, appendicitis, carcinoid tumour

### INTRODUCTION

FMF is an autosomal recessively inherited disease characterized with the recurrent episodes of inflammation of serosal membranes like peritoneal surface, pleura and arthritis. The genetic analysis of the disease yields mutations of MEFV gene located on Chromosome 16. The ethnic predominance of individuals living in Mediterranean and Middle East countries is obvious with a male/female ratio of 2/1. FMF affects certain ethnic groups mainly Jews, Turks, Arabs and Armenians and is caused by mutations in MEFV gene, which encodes pyrin (Onen, 2006). Patients usually admit to hospitals with recurrent abdominal pain mimicking appendicitis due to peritonitis and often have appendectomies after negative explorations. Abdominal FMF attacks resemble the clinical presentation of acute abdomen, with severe abdominal pain and rigidity, but in FMF symptoms always resolve spontaneously (Simon *et al.*, 2005). It is important to distinguish these regular pain episodes from other reasons in order to prevent life-threatening complications.

Acute appendicitis is one of the most frequently performed operations of general surgery. Appendectomies performed for the postoperative diagnosis of acute appendicitis reveals about 85% of the cases. Fifteen percent of the laparotomy or laparoscopies are due to other causes of peritonitis

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such as FMF. The diagnosis of acute appendicitis in a patient with FMF is really hard but it is obvious that an FMF patient has the same risk of developing appendicitis as the others. As a consequence the most dreadful and fatal entity in a FMF patient is the misdiagnosis of acute appendicitis.

Carcinoid tumors are one of the rare tumors of the appendix which is usually diagnosed incidentally during appendectomies performed for acute appendicitis. Appendectomy is performed in cases of carcinoid tumors less than 2 cm in diameter without serosal and mesoappendix infiltration of tumors located anywhere on the appendix other than radix.

Herein, we report a case of an FMF patient with perforated appendicitis carrying an adenocarcinoid tumor on it. We would like to emphasize that surgeon should always approach FMF patients with great suspicion since the problem is not only misdiagnosing acute appendicitis but rarely the condition might be complicated with a malignancy, as well.

### CASE REPORT

A 44 years-old male admitted to our emergency department suffering from diffuse abdominal pain and fever for a week. His previous medical history revealed that he had recurrent episodes (attacks) of fever, arthritis and abdominal pain weekly or monthly for 15 years. Furthermore, his sister was diagnosed to have Familial Mediterranean Fever and died as a result of chronic renal failure 11 years ago. Vital signs were as follows; pulse rate: 130  $\text{min}^{-1}$ , arterial blood pressure: 130/70 mm. Hg body temperature: 38.1C and respiratory rate: 24  $\text{min}^{-1}$ . Decreased bowel sounds, distention, diffuse abdominal pain, involuntary guarding and direct and indirect rebound tenderness in right lower quadrant was present in his physical examination. There was nothing significant in his laboratory findings except a mild leukocytosis with a white blood cell count of 9900  $\text{mm}^{-3}$ . Free air under right diaphragm (pneumoperitoneum) was detected on upright chest x-ray. Following a suitable resuscitation and preparation, patient was emerged to the operation room with the diagnosis of gastrointestinal perforation (perforated viscus). He was found to have perforated appendicitis; a standard appendectomy was performed without any complication and was discharged from hospital on the fifth postoperative day. During his hospital period he was subjected to missense mutation analysis of M680I, M694V, M694I, V726A and E148G of MEFV gene which is proposed to be responsible for FMF and detected to carry M680I, M694V and E148G mutations as compound heterozygote fashion. Histopathologic examination of the specimen was reported be adenocarcinoid tumor (goblet cell carcinoma) with resection margins negative for tumoral infiltration. Histological appearance of the tumor revealed atypical cells with eosinophilic cytoplasm, prominent nucleoli and pleomorphic large vesicular nucleus in desmoplastic stroma. Many small abortive gland like structures in mucine lakes were visualized (Fig. 1, 2).

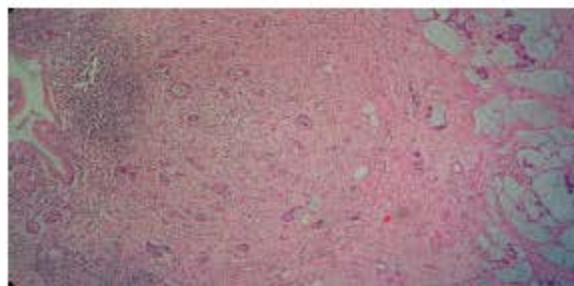


Fig. 1: Infiltration of mucosa and submucosa with goblet cells and mucine lakes

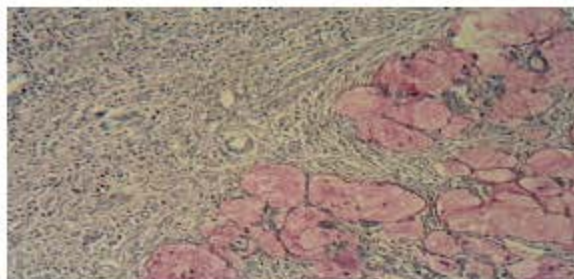


Fig. 2: Mucine stained with mucicarmine

He underwent an interval right hemicolectomy and was back to work in 20 days. Pathological examination of the hemicolectomy material was tumor free.

### DISCUSSION

FMF is an inflammatory disease affecting serosal and synovial membranes. The diagnosis of the disease is usually during childhood; 60% before age of 10, 90% before age of 20 (Gedalia *et al.*, 1992). Attacks can last hours to days. Tel-Hashomer Diagnostic criteria can be used for clinical diagnosis. Present case carries 2 major and 2 minor criteria. The nonspecific clinical manifestations and the lack of accurate diagnostic tests usually direct patients to explorative laparotomies or laparoscopies. The other frequent morbidities of the disease are arthritis, infertility, miscarriages and nephrotic syndrome. Amyloidosis (AA variant) seems to be the major cause of the nephrotic syndrome although other non-amyloid cases are reported. Patients can progress to end stage renal disease and die like the sister of our patient (Ben-Chetrit and Backenroth, 2001). Amyloidosis and the frequency of the attacks can be decreased by using colchicine (Zemer *et al.*, 1986). The genetic mutations of Mediterranean fever (MEFV) gene is cloned on the short arm of chromosome 16 in 1997 independently by International FMF Consortium and the French FMF Consortium (The French FMF Consortium. *Nat Genet*, 1997a, b).

The genetic analysis of our patient yields the mutations of M680I, M694V and E148G. M694V mutation also known as mediterranean mutation is the most common mutation. Yalçinkaya *et al.* (2000) reported the frequencies of the mutations of Turkish patients as 41% for M694V, 16% for M680I. The compound heterozygotic mutations are frequent in Turkish population.

Diagnostic operations are frequently performed for patients suffering from FMF and the operations are usually negative laparotomies. The frequency of negative laparotomies discourages the surgeons for the decision of the operation and the FMF patients suffering from real surgical problems are generally late on the course of the disease. The perforated appendicitis of our patient is one of these examples.

Adenocarcinoid tumors carry the histological features of both the carcinoid tumors and adenocarcinomas (Warkel *et al.*, 1978). The most frequent site of occurrence the adenocarcinoid tumors are appendix. The other possible localizations are gastrointestinal system, biliary tract and the urinary tract (Kanthan *et al.*, 2001; Levendoglu *et al.*, 1990). Goblet cell carcinoid tumors are more aggressive than classical carcinoid tumors although metastases are rare (Butler *et al.*, 1994; Chin and Quzilbash, 1979). The appendicular adenocarcinoid tumors are generally diagnosed in the pathologic examinations of appendectomy specimens operated for other diagnosis. In most cases it is not possible to observe a well-defined mass macroscopically (Bak and Asschenfeldt, 1988). The histopathological

characteristics of goblet cell carcinoids are sparing of the mucosa with infiltration of submucosa and muscularis mucosa. Cells are distended with mucine and have a crescentic nuclei but also with eosinophilic cytoplasm resembling classic carcinoid in some cells (Kanthan *et al.*, 2001; Pahlavan and Kanthan, 2005).

These different characteristics of the adenocarcinoid tumors cause different opinions about the surgical treatment. Some authors recommend appendectomy alone for the tumors without cecal involvement and low grade tumor histology (Varisco *et al.*, 2004). The general consensus for the indication of a right hemicolectomy is cellular undifferentiation, increased mitotic activity, involvement of the base of the appendix with cecal wall infiltration, lymph node metastasis and tumor size greater than 2 cm (Pahlavan and Kanthan, 2005). As the diagnosis is often after the pathologic examination of the appendix, an interval hemicolectomy is performed.

The perforated appendix with 3.5×2 cm tumor size necessitated right hemicolectomy in our patient.

This is an interesting case of adenocarcinoid tumor in a patient suffering from FMF and operated for perforated appendicitis, as we could not find any example in the literature carrying three diseases simultaneously. The crucial point of our case is not only the association of FMF and perforated appendicitis as a consequence of late hospital admission, but presence of a malignancy that predicting the patients survival, as well. In conclusion, surgeon should be alerted in every attack of an FMF patient, since delay in diagnosis might cost a life. Moreover, every appendectomy specimen should be examined meticulously, since patients might require extended surgical interventions in case of malignancies.

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