

AA amyloidosis and pyrin gene mutations

To the Editor: AA amyloidosis may develop in an otherwise asymptomatic case of familial mediterranean fever (FMF) as a presenting first symptom of the disease. This form of the disease is called phenotype II.^{1,2} This suggests that amyloidosis is rather a direct disease-associated condition rather than a complication of a more severe disease state. This hypothesis is further supported by observations of the role of the mutated protein in FMF in inflammatory processes and apoptosis.³ Recently, Atagunduz et al reported an increased frequency of mutations of the MEFV gene both in FMF and non-FMF associated amyloidosis of AA type in Turkey.⁴ However, in their study they did not report any phenotype II FMF case despite a well-known high frequency of FMF in this country. An increased frequency of MEFV mutations in the population seems also to be the case in Italy⁵ and Cyprus⁶ Interestingly, neither of these two surveys encountered phenotype II cases in the populations of Italy⁵ and Cyprus (Deltas, respectively).

During the last years we tested in Athens for pyrin gene mutations, 4 cases were referred to us with an established diagnosis of AA amyloidosis without any evidence for a predisposing factor (e.g., inflammation). The molecular test applied and the findings indicating a diagnosis of AA amyloidosis have already been reported.^{7,8} Several parameters of these cases are shown in Table 1. It is evident that all four cases tested carry pyrin gene mutations with three compound heterozygotes and one heterozygote.

Table 1. AA amyloidosis cases tested for pyrin mutations.

| Case no. | Origin | Sex | Age (y) | Mutation |
|----------|--------|-----|---------|-------------|
| 1 (7) | Greek | M | 50 | V726A/M694V |
| 2 (8) | Greek | F | 65 | M680I/M694V |
| 3 | Greek | F | 45 | E148Q/M694V |
| 4 | Greek | F | 80 | -/M680I |

Interestingly, we were recently referred one further case with a clinically 'definite' FMF diagnosis (according to the Tel-Hashomer diagnostic criteria) in whom only one FMF associated MEFV gene variation was found, namely M694V. This case is currently under investigation for a persisting proteinuria that points to some type of nephropathy. All amyloidosis cases without any evident predisposing factor turned to be either FMF cases (phenotype II) or disease carriers.

A recording system for all cases of AA amyloidosis seems necessary. Molecular study for MEFV gene point mutations in every amyloidosis case may shed further light on this putative predisposing factor.

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5-Fluorouracil-induced vasospastic angina

To the Editor: The antimetabolite 5-fluorouracil (5-FU), which is frequently administered as chemotherapy for various malignancies, can rarely cause stable angina, arrhythmias, myocardial infarction, and sudden death.¹ The underlying mechanisms of cardiotoxicity are not yet fully known, although coronary vasospasm may be responsible.^{2,3} Chest angina has been noted both on the initial and the second and third

course. Mortality may increase when courses are repeated. We describe a patient who developed chest angina, likely of vasospastic origin, during treatment with 5-FU. A 31-year-old male had metastatic colorectal adenocarcinoma diagnosed in May 2003. He had no history of cardiac disease. On June 2, a peripheral venous catheter was implanted and an intravenous infusion of 5-FU (425 mg/m² IV bolus daily on days 1 to 5) was started. He received 2 cycles of chemotherapy (5-FU plus leucovorin), with a cumulative 5-FU dose of 2890 mg. At the end of June 2003, on the third day of the second cycle, the patient suffered from typical chest pains and was referred to our clinic for a cardiologic evaluation. He had a similar history of symptoms on the first course of 5-FU. Physical examination and two-dimensional echocardiography were normal. The electrocardiogram (ECG) at rest showed ST segment elevation in leads DII, DIII, aVF, V5, and V6. Symptoms resolved after nitroglycerin infusion during the tenth minute, the ST elevation returned to baseline and negative T waves occurred (Figure 1). Negative T waves return to normal after three days (Figure 2). Cardiac enzymes were normal. Hemoglobin was 13 g/dL. Serum electrolytes and renal function were normal. The negativity of the test and absence of chest pain after 5-FU interruption indicates the absence of chronic, flow-limiting coronary stenosis. For complete confirmation, coronary angiography was done on the second day of angina and found as normal. Intracoronary nitroglycerin was not used during angiography. Three days later, the patient was completely asymptomatic and his

ECG at rest was normal. The patient remained asymptomatic and the ECG was normal in clinical follow up.

Cardiotoxicity has been reported as a side effect of anticancer drugs, particularly in patients undergoing anthracycline antibiotics. The cardiotoxicity of 5-FU also has been known for years, but the drug is not familiar to many physicians. There are a few case reports of angina

pectoris and even myocardial infarction associated with 5-FU.^{4,5} The mechanism of cardiotoxicity is uncertain and speculative. In vitro studies have shown an endothelium-independent vasoconstriction of vascular smooth muscle cells, involving activation of protein kinase C. Exercise is a known potential vasoconstrictor trigger, possibly through noradrenergic sympathetic stimulation. Symptoms were associated with

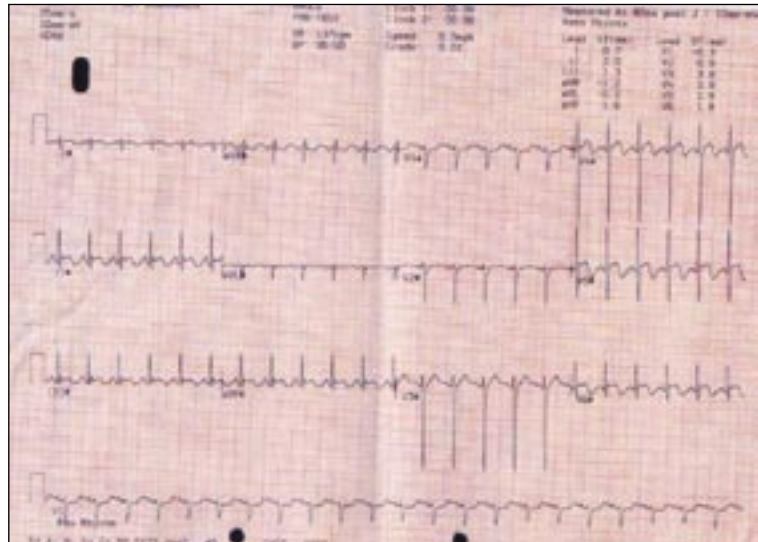


Figure 1. ST elevation returned to baseline and negative T waves occurred after nitroglycerin infusion.



Figure 2. Normal electrocardiogram after three days.

the initiation of 5-FU treatment, which has a recognized potential to cause spasm, and disappeared after its cessation. The angina is occasionally delayed to 3 to 18 hours after 5-FU injection. Porta et al. found high plasma levels of endothelin-1 (ET-1), a potent natural vasoconstrictor, in two patients who experienced two of the commonest clinical manifestations of 5-FU-induced cardiac toxicity, i.e., angina pectoris and chronic heart failure.⁶ They, therefore, proposed ET-1 as the ultimate mediator of this toxicity, even though the mechanism of ET-1 increase in peripheral venous blood is still unknown. Finally, another important question still remains unresolved: is the release of ET-1 from normal coronary endothelial cells the prime cause or simply the consequence of 5-FU-related cardiotoxicity? Spasm can be triggered by an array of stimuli acting on different receptors, such as ergonovine, histamine, serotonin, and acetylcholine, as well as by severe alkalosis by handgrip and cold pressor tests. Thus, localized postreceptor alterations that make the coronary artery smooth muscle hyperactive to a variety of constrictor stimuli appear the likely pathogenetic mechanisms for the typical clinical syndromes of variant angina.⁷ In addition, chest pain associated with 5-FU has several characteristics that are incompatible with coronary artery spasm, e.g., inadequate efficacy of a calcium-channel blocker and a slow increase in cardiac enzyme levels. Mizuno et al. experienced a case of 5-FU-induced cardiotoxicity, which showed clinical findings consistent with acute myocardial infarction. Based on the clinical findings, coronary angiography, and left ventricular

angiography in a prolonged attack, they concluded that the cardiotoxicity in this case was not due to ischemia caused by coronary artery spasm.⁸ Keefe et al. reported that of 910 patients who treated with 5-FU, 5 developed life-threatening toxicity consistent with coronary artery spasm for an incidence of 0.5%.⁹ Some reports suggest that more invasive tests were not clinically indicated.¹ Although angiographic confirmation of vasospasm was not obtained, ST-segment elevation during the early recovery phase of an exercise stress test is considered a hallmark of transmural ischemia of vasospastic origin.² A history of cardiac arrhythmias or of syncope occurring during angina, or immediately after, is particularly suggestive of vasospastic angina and is a strong indication for cessation of 5-FU and for prescribing full antivasospastic therapy. A high index of suspicion for cardiotoxicity must be maintained when the drug is administered, especially in the presence of heart disease and concomitant radiation therapy.¹⁰ Concomitant chemotherapeutic agents, received by all the affected patients, may have a contributory effect. Cardiotoxicity seems to be completely reversible, particularly in patients without underlying cardiac disease. The patients should be informed about the symptoms and the condition recognized and managed immediately.¹¹ As beta-blockers are totally ineffective, antivasospastic therapy should be based on a full dose of calcium antagonists and also of nitrates, administered to cover the time when attacks recur, to avoid the development of tolerance. Myocardial infarction and pericarditis should be clarified in the differential diagnosis of ST

elevation. This report of vasospastic angina by 5-FU emphasizes the importance of cardiac events during 5-FU. In addition, chest pain should alert the physician during treatment with this agent.

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