Recurrent pericarditis: mysterious or not so mysterious?

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This editorial refers to 'Pretreatment with corticosteroids attenuates the efficacy of colchicine in preventing recurrent pericarditis: a multi-centre all-case analysis† by G. Artom et al., on page 723

Recurrent pericarditis encompasses two forms: (i) the intermittent type with widely varying symptom-free intervals without therapy; and (ii) the incessant type, in which the discontinuation of anti-inflammatory therapy ensures a relapse. Clinical symptoms are characteristic for pericardial disease but are non-specific; they include pre-cordial pain, often associated with a pleuritic component. Fever, pericardial friction rub, dyspnoea, elevated C-reactive protein or sedimentation rate, and electrocardiogram changes are common. Massive pericardial effusion or cardiac tamponade or constriction are rare events. Several mechanisms have been suggested to explain recurrence: (i) insufficient dose and/or insufficient treatment duration of anti-phlogistics or corticosteroids in autoimmune or ‘idiopathic’ pericardial disease; (ii) early corticosteroid treatment causing augmented viral DNA/RNA replication in the pericardial tissue leading to increased viral antigen exposure; (iii) re-infection; and (iv) exacerbation of an underlying connective tissue disease.1

For the symptomatic management of recurrent pericarditis, the ESC task force on the management of pericardial diseases,1 in accordance with international expert opinion,2 has recommended exercise restriction and the therapeutic regimen used in acute pericarditis with NSAIDs, whereby indomethacin should be avoided in the elderly due to its flow reduction in the coronaries. It emphasized the particular role of colchicine, which showed benefit even in cases in which NSAIDs and corticosteroids failed to prevent relapses3,4 and recommended 2 mg/day colchicine in refractory cases (level of evidence B, indication class I). It recommended excluding viral or bacterial infection as causes of the relapse. This can be done best by PCR from endo- or epicardial tissue or the effusion. Only then should a patient in poor condition, or in frequent crisis, receive corticosteroids (1–1.5 mg/kg prednisone for at least 1 month; level of evidence C, indication class IIa). The task force pointed out that a common mistake, which is to use a dose too low to be effective or to taper the dose too rapidly, should be avoided. In refractory cases, azathioprine (75–100 mg/day) or cyclophosphamide can be added. Pericardectomy is indicated in highly symptomatic cases resistant to medical treatment.

In their multi-centre, all-case analysis, Artom Galit et al.5 investigate the efficacy of colchicine in preventing relapses of pericarditis. The authors aggregated 119 patients and followed them up. They found, by multivariate regression analysis, that only previous corticosteroid therapy and male gender were independent risk factors for recurrence. They conclude that pre-treatment with corticosteroids may attenuate the efficacy of colchicine in preventing recurrent pericarditis. These aggregated data are of great interest to the cardiologist; the database is relatively large for this form of pericarditis—it comes from six cardiology centres with a worldwide reputation on pericardial disease—and underlines previously published data on the efficacy of colchicine in recurrent pericardial effusion.4,5 Whereas the beneficial role of colchicine has been implemented in the ESC taskforce recommendations,1 the aforementioned results reach farther than simply stating the beneficial effect of colchicine in recurrent pericarditis. They indirectly imply that pre-treatment with corticosteroids for the initial and recurrent effusions might be disadvantageous, since their use appeared to attenuate the...
Effect of colchicine at the time of recurrence. Such a strong statement would necessarily have an impact on treatment recommendations in acute and chronic pericarditis. Whereas I share the opinion that the unreflected use of cortisone in patients with pericarditis should not be recommended, I would object to a generalization, which has not been made by the authors but could prematurely be deduced from their data, that corticosteroids should no longer be used in chronic or recurrent pericarditis. For such a generalization, the data presented by Artom et al.\(^5\) are not sufficient. The reasons are:

(i) This study is ‘only’ a multi-centre retrospective registry. A prospective design would have been advisable,\(^6\) but their data are the best that we can have on this disease today.

(ii) All the modes of action of colchicine are not yet clear. It is well known to have potential as an antiinflammatory drug but works on a much broader base than the cox-2 inhibitors, which have recently been withdrawn from the market because of an increase of myocardial infarction in the study population. Colchicine has been known to inhibit mitoses in the cell nucleus, it binds to tubulin, inhibits the function of polymorphonuclear cells, and interferes with the transcellular movement of collagen.\(^1,2\)

(iii) There are side-effects of colchicine to be considered and several of them have never been adequately reported. Whereas diarrhoea is well known when colchicine is given at high doses (2 mg/day or more), other side-effects are not. In our Marburg Pericarditis Registry, moderately increased liver enzymes were observed in 7% of patients. A reversible increase of the tumour marker Ca 19-9 was found fairly frequently in 11% of patients (unpublished data on file).

(iv) Artom et al.\(^5\) have not addressed a very relevant question in a recurrent disease: the underlying cause or aetiology of the disease itself. It has also been neglected by many cardiologists and is rarely discussed in clinical textbooks. To state it very clearly: ‘idiopathic’ is very often just an excuse for not using the right tools in the analysis of the respective disease. This also applies to recurrent inflammation when the causative agents, such as cardiotropic viruses or (peri)cardiotropic bacteria, should be identified before we treat the patient. The common belief that idiopathic is an equivalent of autoimmune pericarditis is based on assumption but not modern molecular methods.

If PCR is used for the assessment of cardiotropic agents in the effusion, the epicardial or endomyocardial biopsy of patients with pericarditis as in the Marburg registry from 1989 to 2002 (n = 260, 156 male, age 56.5 ± 14.9 years) the distribution is as follows: viral aetiology in 13.5%, bacterial aetiology in 9.3% (2.3% Borrelia burgdorferi, 3.7% tuberculosis, 3.3% other forms), lymphocytic effusions in 9.8%, autoreactive effusions in 12.6%, malignant and radiation induced forms for the rest (data from references 7–9). Recurrent peri-cardial effusions were found in the last 5 years in only 15 out of 248 patients who underwent sclerosing intra-pericardial treatment with triamcinolone in addition to oral colchicine treatment in non-malignant pericarditis. In 5 of the 15 cases viral aetiology was missed at the time of initial analysis and only detected by PCR in the effusion or the epicardial biopsy at the second attack. Enterovirus, adenovirus, cytomegalovirus, Parvo B19, and hepatitis B were each recovered once at the time of recurrence. This clearly shows that missed viral aetiology may contribute to recurrent pericarditis. In these cases, corticosteroids could promote viral replication and thus prolong the treatment course. It remains speculative, however, what the true percentage of undiscovered viral aetiology has been in the multi-centre all-case study of recurrent pericarditis by Artom et al.\(^5\) One might suspect that the distribution of aetiological agents in pericarditis is not so different from the spectrum found in inflammatory myocardial disease.\(^10\)

Undiscovered microbial aetiology is well in line with the comments\(^11\) that have been made on the American Myocarditis Trial.\(^12\) One major criticism with respect to the ineffectiveness of immunosuppression was that the RNA and DNA of cardiotropic agents in the endomyocardial biopsies were not carried out.

Finally, if any anti-inflammatory therapy is terminated too early, recurrence may be pre-programmed,\(^1\) independent of the drug that has been used. There may be a tendency to taper prednisone treatment earlier than colchicine due to the well-known steroidal side-effects. But as Adler et al.\(^14\) have already pointed out in 1999, the discontinuation of colchicine treatment is also a trigger for recurrent pericarditis.

References