Acute Pericarditis: Aetiologic Diagnosis and Practical Aspect of the Management

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Abstract: Pericarditis is an uncommon pathology that represents 0.1% of patients hospitalized for chest pain with a wide etiological spectrum and whose cause is uncommonly highlighted. In order to determine the incidence of specific acute microbiological or autoimmune pericarditis and identify subsets of patients with a higher incidence of specific etiologies; and analyze the conformity of the management of acute pericarditis according to the recommendations, a retrospective inclusion of all patients admitted to our hospital from January 2010 to December 2018 with the diagnosis of acute pericarditis was conducted. Data concerning clinical, paraclinical and treatment items were collected. Ninety-nine patients were included. Specific etiologic exams were completely conducted in 63.6% of the patients. There was no link between the decision to conduct etiology exams and the age, gender, a history of acute pericarditis or relapse. There was a trend between an elevated CRP and the realization of the kit. There was a statistically significant link between the achievement of etiologic exams and the presence of severity criteria or the presence of a pericardial effusion. An etiology was found in 52.4%, more frequently microbiological (viral and *Mycoplasma pneumoniae*). Approximately 85.9% of all patients were hospitalized. Treatment was in accordance with the

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recommendations in 76.8%. Despite the percentage of microbiological etiologies found, it does not impact the therapeutic strategy. The criteria for hospitalization must be better suited since half of those hospitalized after the european society of cardiology (ESC) 2015 recommendations had no need to be. However, monitoring after discharge is not clearly defined by learned societies. (Curr Probl Cardiol 2021;46:100769.)

Introduction

Pericarditis is an infrequent pathology since it is diagnosed in 5% of patients consulting emergency department for chest pain not related to an acute coronary syndrome and represents 0.1% of patients hospitalized for chest pain.[1] Furthermore this disease has a wide etiological spectrum[2] and whose cause is not often identified, 22% in an American study for example.[3] Thus, an Italian study from 2004 recalls that viral etiology is often presumed but very often not sought because it constitutes a non-negligible and rather time-consuming expense whereas in the absence of risk factors for severe pericarditis,[1]neither the performance of tests to establish a specific etiological diagnosis nor hospitalization of the patient is necessary in most cases.[4] In fact, if the routine assessment of a suspicion of pericarditis should contain an ECG, chest x-ray, ETT as well as a biological assessment (CRP, White blood cells, Troponin, creatine phosphokinase (CPK)), the need for routine etiological research for all pericarditis is controversial (5).

Moreover it is described that serologies and cultures are unreliable.[6] As for the microbiological spectrum, when it could be identified, it seems to differ from country to country, thanks to a "local ecology."[4,7,8] In fact, a 2004 French study recommends that a systematic approach confirms the etiological diagnosis in a noninvasive way in the majority of cases and thus significantly reduces the number of cases labelled "idiopathic" and allows the identification of curable causes such as Mycoplasma, Q fever, Toxoplasmosis, Hypothyroidism, and anticytoplasm antibodies (ANCA) in this work.[9]

The main objective of this study was to determine the incidence of specific acute microbiological or autoimmune pericarditis and to identify subsets of patients with a higher incidence of specific etiologies. The secondary objectives were to analyze the compliance of acute pericarditis management prior to 2015, when hospitalization was largely supported by monitoring the effectiveness of treatment and the occurrence of complications and initial treatment based solely on Aspirin and after 2015,

when hospitalization became reserved for a few risk factors for poor prognosis and treatment on the combination of aspirin and colchicine.

Methods

The series included retrospectively all patients admitted to our hospital from January 2010 to December 2018 with the diagnosis of acute pericarditis. Patients with chronic constrictive pericarditis or ongoing neoplasia were excluded. Acute pericarditis was retained according to the CIM10 classification. Information regarding these items were collected: presence of fever, chest x-ray film, electrocardiogram, echocardiogram, red and white blood cell count, CRP, fibrinogen, and any etiologic exam realized in our hospital and included in our "pericarditis kit": blood cultures, serologic test for *Mycoplasma pneumoniae*, CMV, EBV, *Coxiella burnetti*, hepatitis C, HIV, Toxoplasma, Parvovirus B19, Thyroïd hormone, antinuclear antibodies, rheumatoid factor, and PCR for Enterovirus. Data concerning the treatment according to the guidelines of the moment and management after discharge were also collected.

Statistical analysis: Continuous data are reported as mean ±SD and categorical data as percentages. The χ^2 test was used to compare categorical data. Differences were considered significant at P values<0.05 with Sphinx IQ2 software. The study was approved by the ethical instance concerned.

Results

Epidemiologic Characteristics

A total of 99 patients aged 16-86 years (46.2 years [±17.8 years]) and with 65.7% of men were included. A history of prior acute pericarditis was present in 15.2%, and a relapse episode in 5% (defined as a new painful episode appearing after 4 weeks of the first episode and before 3 months).

Clinical and Paraclinical Features

The symptom always present was, not surprisingly, suggestive chest pain. Fever was present in 15.2% with an average of 38.3˚C. CRP was normal in 20.2%, moderately increased in 39.4% (from 5 to 50 mg/L) and increased in 40.4% of the study (>50 mg/L). Concerning white blood cells, it was elevated in 42.4% and in this case the standardization at J1 was of 40.5%, or 59.5% of white blood cells still high. Fibrinogen was not done in 3% of the cohort, normal in 28.3%, moderately increased in 29.3% (from 4 to 6 g/L) and elevated in 39.4% of our patients (> 6 g/L).

A chest x-ray film was performed in 74.7% of our patients and was always normal. The ECG was present in 100% of our cohort and was compatible or suggestive of acute pericarditis in 50.5%. The echocardiography was not done in 5.1% of our cohort, normal in 50.5% whereas a pericardial effusion was found in 44.4%.

Specific etiologic exams were completely conducted in 63.6% of the patients. It concerned 74.2% of patients before 2015 (49/66) and 42.4% of patients after 2015 (14/33), and this difference was statistically significant ($P = 0.01$).

There was no link between the decision to conduct etiology exams and the age, gender, a history of acute pericarditis or relapse. There was a trend between an elevated CRP >50 mg/L and kit's realization ($P = 0.05$). There was a statistically significant link between the achievement of etiologic exams and the presence of severity criteria ($P = 0.03$) or the presence of a pericardial effusion ($P < 0.01$).

When exams were realized, an etiology was found in 52.4% of the cases (33/63). Six presented with an autoimmune pathology including 4 with a microbiology positivity: 1 patient had a rheumatoid factor and a Enterovirus PCR and a Parvovirus B19 serology all at the same time (3%), 3 patients had antinuclear antibodies anti SSA and a Mycoplasma serology at the same time (9%), 2 patients had antinuclear antibodies (6%). Twenty-seven had and isolated microbiological positivity: 1 patient had an EBV serology then an EBV PCR (3%) and 26 patients had a positive Mycoplasma serology alone (78.8%). There was no statistically significant link between one of the etiologies mentioned above and age, gender, history of pericardial effusion or relapse, fever, value of CRP, presence of a pericardial effusion, or a correlation between before and after 2015.

Approximately 85.9% of the total cohort (85/99 patients) were hospitalized. If the trend was to hospitalize young patients (40% of hospitalizations concerned patients under 40 years and 37.6% patients from 40 to 60 years), hospitalization was statistically significantly correlated with an elevated CRP >50 mg/L ($P < 0.01$) or presence of severity criteria ($P = 0.02$). There was no link between gender, a history of prior acute pericarditis or a relapse, and decision to hospitalize patients.

For patients before 2015 european society of cardiology (ESC) recommendations (n = 66), hospitalization was decided in 90.9% of the cases (60/66 patients). ESC recommendations in 2004 were mentioning that hospitalization was warranted for most people to determine the aetiology, observe for tamponade and start anti-inflammatory and symptomatic treatment.

2015 recommendations defined severity criteria suggesting hospitalization: fever >38°C, subacute course, pericardial effusion>20mm, failure to respond within 7 days to nonsteroidal anti-inflammatory drugs, myopericarditis, immunodepression, trauma and oral anticoagulant therapy. For patients after 2015 (n = 33), the presence of at minimum 1 severity criterion was found in 33.3% (11/33 patients). However, 25 patients were hospitalized (75.8%) whereas 11 should have been because they had at least 1 severity criterion. Concerning the 56% of patients hospitalized without any severity criteria (14/25), they were all under 35 years and 95% were men. CRP was normal in 26.3% of the cases, moderately elevated in 57.9% and elevated in 15.8%. ECG was abnormal in 52.6%, echocardiography found a minimal effusion (<20 mm) in 26.3%.

The exit treatment was in accordance with recommendations in 76.8%. For patients before 2015, treatment was in accordance with 2004 ESC recommendations in 78.8% of the cases. For patients after 2015 and ESC recommendations of this particular year, 72.7% of the treatment was conform. Globally, when it was not, it concerned most of the time an insufficient treatment time (30%) or insufficient dosage (26%), abusive association of drugs (21.7%), missing drug in treatment regimen (17.4%) or both insufficient treatment and dosage (8.7%). Note that a same patient could combine several prescription errors.

After consultation in the emergency room or hospitalization, a cardiological consultation with an ECG was planned in 43.4%, respectively in 40.8% and 46% depending on whether the ECG was normal or not (*P*not significant). An echocardiography was controlled in 38.4%, in 71% when there was an initial pericardial effusion and in 29% when there was no effusion or when first echocardiography had not been made ($P < 0.01$).

Discussion

Epidemiological data from our study included a rather young population (46 years on average), male-oriented (2/3 sex ratio), which is consistent with the literature.[1,7,10,11] Regarding clinical and paraclinical elements, we found that hyperthermia was inconstant since present in 15% of cases. While hyperthermia is described in literature without any notion of proportion for some,[12] others indicate that it is more often present in cases of bacterial origin.[13] In Imazio and al 2007 work, hyperthermia was found in 9.3% of patients with no specific etiology objectified and in 42% in the other group,[10] which we did not highlight in our study since hyperthermia was found in 20% of patients with or without recovered etiology. Inflammatory markers in our study population were a good

aid in diagnosis of acute pericarditis and assessment of the clinical picture since CRP was high in nearly 80% and Fibrinogen in 70% of the cases, this result being similar to literature.[12-14] As for leukocytes, their rise was found in 40% of cases but with a normalization on day 1 in 40% against 59.5% which remained abnormal on day 1, the normalization being probably due to the phenomenon of demargination during the balance of entry. The leukocyte's elevation is also described in literature.[12] Chest x-ray was of little interest since it was always normal (demonstrated in literature[12] and was performed in 2/3 of our cohort). But bibliography clearly points out that it must be part of the systematic assessment, if only to eliminate differential diagnoses.[5,15] The ECG showed signs of acute pericarditis only in 50% of cases. Literature does not provide any data on this subject, but indicates that sometimes the ECG does not find any particular sign.[6,16] As for echocardiography, it objectified pericardial effusion in 44% of our workforce compared to 60% in literature.[17]

An etiological assessment called "pericarditis kit" was taken from 63.6% of our cohort. Again, there seems to be a trend between high CRP and kit's implementation. On the other hand, there was a statistically significant link between kit's production and the presence of a severity criteria, as well as with presence of a pericardial effusion (whether it was greater or less than 20 mm). This kit's realization was statistically linked to management before 2015 since the 2004 recommendations recommended a wider hospitalization, which allowed time to start etiological research. In literature, carrying out an etiological assessment varies enormously on this theme. For example, if the 2004 ESC recommendations indicate that hospitalization must be decided for most patients in order to carry out, among other things, an etiological assessment,[18] the 2015 guidelines explain that diagnostic and therapeutic value of systematic etiological research is low.[1] Thus, a 2004 Spanish study indicates that for patients with comorbidities and in absence of pericarditis's improvement within 1 week of starting treatment, antinuclear antibodies, antibodies against rheumatoid factor as well as ECBC or bronchial aspiration looking for mycobacteria should be practiced.[15] According to other authors, routine etiological assessment including viral cultures and antibodies titration is not usually useful, especially when presence of a viral infection does not alter management.[4,13,16] Others believe that search for HIV, antinuclear antibodies, rheumatoid factor, tuberculin test, or tuberculin quantiFERON should be considered only in immunocompromised patients[13] or a general etiological assessment (infectious and autoimmune) in patients presenting a risk factor for severity.[5,17] Conversely, in a 2004 French study of patients with pericardial effusion(whatever the

abundance), it was recommended to carry out a systematic etiological research to significantly reduce the number of cases labeled "idiopathic" and highlight curable causes such as Q fever, Mycoplasma, Toxoplasmosis, hypothyroidism and antinuclear antibodies, serological tests for other causes being negative in this study.[9] German or Italian studies remind us that, in case of viral origin, viral infection is limited and often does not require specific treatment.[8,17]

In our study, when it was carried out (2/3 of the cases), etiological balance came positive almost once in 2 (52.4%), which is higher than data in literature at 22%[3] or 31%.[7] Some etiologies came back for us in very low proportions, this is the case of anti SSA antibodies, rheumatoid factor, Enterovirus, Parvovirus B19, EBV, antinuclear antibodies while in other works percentages of autoimmune diseases are higher.[7,16] Conversely, for our cohort, Mycoplasma serology was positive in almost 80% of the etiologies found and it could be positive in association with one of the etiologies mentioned above. Two French studies in 2003 and 2004 also objectified a significant proportion of Mycoplasma.[7,9] However, positivity to Mycoplasma did not lead to a specific antibiotic treatment as patients improved under anti-inflammatory treatment. Note that no patient resented an etiological table relating to a bacterial origin or hepatitis C, HIV, *Coxiella burnetti*, Toxoplasma, or dysthyroidism. However, this same 2004 Marseilles study (very close geographically to our center) had objectified a significantly higher proportion of hypothyroidism and Q fever in their population compared to another French region. Note however that in this study of 138 patients, the entire cohort presented pericardial effusion,[9] which was not always the case for our workforce (as a reminder, 44.4%). Another 2006 French study on pericardial effusion reported a specific etiological diagnosis in 14% of patients.[19] It is also probable that etiologies found depend on territory's microbiological ecosystem.

We have not objectified any link between existence of a specific etiology and patient's epidemiological or clinical profiles. This is similar to a 1995 American study in regards to gender and history of pericarditis.[3] However, this work found a specific etiology in younger patients as well as those with an unfavorable clinical course after medical treatment. Similarly, Imazio et al, in 2004, in a prospective cohort of 300 patients, demonstrated that patients with a clinical or ultrasound risk factor were significantly associated with a specific etiology,[4] identical result found at conclusion of another Italian study of 2010.[6]

Difference in hospitalization between before and after 2015 is due to differences in recommendations for these indications. If 2004 ESC recommendations advocated that hospitalization was justified for most

patients (91% in our study of patients before 2015) in order to search for an etiology, monitor the appearance of tamponade and ensure effectiveness of anti-inflammatory treatment,[18] ESC 2015 recommendations defined severity criteria which justify hospitalization for monitoring good clinical and paraclinical development.[1] Of the 33 patients after year 2015 cohort, 25 were hospitalized, 14 of them by excess because they had no criteria for being so. Trend shows that young patients were hospitalized more often (78% of those hospitalized were under 60 years of age). If decision to hospitalize was statistically significantly correlated with presence of a severity criteria, it was also statistically significantly related to a high CRP (>50 mg/L). We could not find similar data in literature.

Exit treatment was in accordance with recommendations in 76.8%, in proportions compared to the 2 recommendations, reflecting a rapid appropriation of changes in modalities of therapeutic regimens. We have not found any data on this point in literature.

After consulting in the emergency department or hospitalization, a cardiological consultation was planned in 43.4% and an echocardiography in 38.4% a fortiori when first echocardiography found a pericardial effusion ($P < 0.01$). Note that recommendations do not indicate any particular follow-up for dry pericarditis or with weak effusion (<10 mm) beyond 7 days, after ensuring effectiveness of anti-inflammatory treatment. For an idiopathic pericardial effusion of average abundance, ultrasound control should be done every 6 months, and every 3-6 months in case of profuse effusion(>20 mm).[1] Another study mentions value of follow-up to ensure effectiveness of treatment and the absence of constrictive sign's appearance, but without specific indication.[20]

But management would benefit from being multidisciplinary with help of an infectious disease specialist and an internal physician, thereby improving etiological research such as curable infections or systemic diseases. In our study, if treatment complies with recommendations, compliance with indications for hospitalization should be improved as shown by our results. However, it is also necessary to better organize follow-up to ensure good progress.

Study limitations: this is a retrospective and monocentric work.

Conclusions

Acute pericarditis is usually managed by emergency physicians for positive and differential diagnosis, established with cardiologist's help, allowing establishment of adequate treatment and avoiding complications. Etiological assessment, encouraged in ESC 2004 recommendations

during a widely recommended hospitalization, is limited in ESC 2015 recommendations to forms with severity criteria, which we found in our study with 2 times less etiological research. It must be recognized that despite high percentage of microbiological etiologies (viral and *M pneumoniae*) found when etiological exams are made in our work, it does not impact therapeutic strategy. There was no statistical correlation between positivity of etiological research and patient's clinical or paraclinical data. ESC 2015 recommendations consolidated anti-inflammatory treatment with use of 2 molecules against 1 alone previously. Our study shows that change in treatment modality was well followed. However, criteria for hospitalization must be better suited since we have established that half of those hospitalized after 2015 had no need to be. However, monitoring of acute pericarditis is not clearly defined by learned societies, which may explain why less than 1 in 2 patients receives specialized monitoring.

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