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Original Article

Recurrent pericarditis in children: Clinical findings and outcomes

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ABSTRACT

Objective: In this study, we aimed to evaluate the clinical findings and follow-up data of children with recurrent pericarditis (RP).

Material and Methods: This study had a retrospective design and included pediatric patients with recurrent pericarditis evaluated between January 2017 to January 2023. The initial diagnosis of pericarditis was made according to the criteria determined in the European Society of Cardiology guideline.

Results: We enrolled 16 children (14 males) with recurrent pericarditis with median age 12.8 (8 – 17) years. Eight patients (50%) presented with fever, pericardial effusion in 11 patients (68.7%). Pericardiocentesis was performed in 9 (56.2%) patients. The median erythrocyte sedimentation rate (ESR); C-reactive protein (CRP) levels at the time of diagnosis were 43 (25-70) mm/h and 107 (61-190) mg/dl, respectively. In total, 16 patients had 36 recurrences during follow-up. The main symptom during the relapses was chest pain, similar to that of the first attack. Four patients (25%) had a history of previous cardiac surgery. Three patients were treated with nonsteroidal anti-inflammatory drugs (NSAIDs) only. NSAID and colchicine were administered to 13 patients. One patient received corticosteroid and one patient received anakinra treatment.

Conclusion: Patients with recurrent pericarditis in childhood have an autoinflammatory phenotype. Furthermore, successful management of patients with recurrent pericarditis requires a teamwork approach involving cardiologists, rheumatologists and clinical immunologists.

Keywords: Autoinflammation, childhood, colchicine, pericarditis

INTRODUCTION

Recurrent pericarditis (RP) is one of the most common pericardial diseases, affecting up to 30% of adult patients suffering from acute pericarditis (1-3). Rheumatic diseases, Familial Mediterranean fever (FMF), and previous cardiac surgery are etiological factors (4). In approximately 70% of pediatric patients and more than 80% of adult patients no specific etiology can be identified and therefore pericarditis is considered idiopathic. In recent years, the underlying cause of idiopathic recurrent pericarditis (IRP) is thought to be autoinflammatory (5-9). The accepted pathogenetic scenario is that infectious agents (mostly viral) trigger the inflammation pathway through different transmissions between the immune system (10). The long-term prognosis of recurrent pericarditis is generally good. However, frequent relapses are one of the most challenging treatment problems and the quality of life in these patients can be seriously affected (11). There are insufficient published studies/data on the management, treatment and prognosis of recurrent pericarditis in children. In this study, we aimed to evaluate the clinical findings and follow-up data of 16 children and adolescents with RP.

MATERIALS and METHODS

This study had a retrospective design and included 16 pediatric patients (14 males, 2 females) with recurrent pericarditis evaluated between January 2017 to January 2023. The initial diagnosis of pericarditis was made according to the criteria determined in the European Society of Cardiology guideline. Patients whose pericarditis recurred at least once, at least 4-6 weeks after the first attack, were included in our series. The diagnosis of recurrent pericarditis was based on the following criteria: previous definitive diagnosis of acute pericarditis and presence of at least two of the four following criteria: typical

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chest pain (sharp and pleuritic, improved by sitting and leaning forward), pericardial rub sound, typical electrocardiography (ECG) changes (diffuse ST elevation or PR depression), and new or worsening pericardial effusion. Patients with confirmed systemic connective tissue and autoinflamatory diseases were excluded from the study. Clinical features of pericarditis during the attacks, ECG changes, number and characteristics of relapses, laboratory findings [genetic analyses for FMF and autoinflammatory disesase, troponin, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level] and treatment records were analyzed. Previous medical history such as heart surgery and comorbidities were recorded. Patients and their parents gave informed consent.

Acute pericarditis (AP) is defined as an inflammatory condition involving the pericardium that has a sudden onset and is characterized by at least two of the following four clinical features: (A) typical chest pain that sharp, pleuritic and increases with inspiration (b) pericardial rub; (c) typical electrocardiographic changes (e.g. diffuse ST elevation or PR segment depression); (d) a new or worsening pericardial effusion (12). For the diagnosis of recurrent pericarditis, a symptom-free period of at least 4-6 weeks was required between the first attack and recurrence (13). “Refractory pericarditis” is pericarditis that recurs despite optimal medical treatment such as colchicine and corticosteroids (3).

Statistical analyses

SPSS (Statistical Package for Social Sciences) for Windows 22.0 (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. The variables were investigated using visual (histogram, probability plots) and analytical methods (Kolmogorov–Smirnov) to determine whether or not they were normally distributed. Continuous variables are presented as mean, standart deviation (SD), median and interquartile range (IQR), while categorical variables are given as numbers and percentages. A p-value of less than 0.050 was considered to show a statistically significant result.

RESULTS

We enrolled 16 children with recurrent pericarditis with median age 12.8 years (8 – 17 years). Diagnostic criteria were pericardial chest pain in 16 cases (100%), pericardial rub in 5 cases (31.2%), ECG changes (widespread ST-segment in 5 cases (31.2%), PR segment depression in 3 cases (18.7%), low voltage QRS complex in 6 cases (37.5%). The ECG was normal in 6 patients (37.5%). Pericardial effusion was detected in 11 patients (68.7%). Eight patients (50%) presented with fever. Mild cardiac tamponade was recorded in 1 patient (6%) during the episodes (Table I).

The mean diastolic thickness of pericardial fluid was 12.5 mm. Pericardiocentesis was performed in 9 (56.2%) patients. The chest X-ray showed cardiac enlargement in 5 (31.2%) patients. The median (IQR) ESR and CRP levels at the time of diagnosis were 43 (25-70) mm/h and 107 (61-190) mg/dl, respectively. ESR and/or CRP values were elevated in all cases.

Table I: Clinical data of the patients in the present study and the other cohorts

Clinical characteristics	Present study*	Raatikka et al. (17)*	Finetti et al. (29)*	Imazio et al. (11)*	Imazio et al. (14)*
Number of patients	16	15	15	110	240
Chest pain	15 (93.8)	15 (100)	13 (87)	103 (93.6)	239 (99.6)
ECG changes	10 (63)	10(67)	13 (87)	49 (44)	60 (25)
Pericardial effusion	11 (69)	15(100)	13 (87)	86 (78)	138 (57)
Pericardial rub	6 (38)	Na	5 (33)	31 (28)	82 (34)
Elevated ESR-CRP	16 (100)	14 (93)	13 (87)	102 (93)	174 (72)
Fever	8 (50)	12 (80)	8 (53)	84 (76)	73 (30)
Tamponade	1 (6)	1 (7)	0	15 (14)	2 (1)
PPS	4 (25)	7 (47)	Na	10 (9)	21 (9)
ANA positivity	1 (7)	1 (7)	Na	18 (16)	103 (43)
NSAIDs	16 (100)	4 (27)	13 (87)	89 (81)	240 (100)
Colchicine	13 (81)	4 (27)	14 (93)	68 (62)	120 (50)
Corticosteroids	1 (6)	11 (73)	15 (100)	70 (65)	16 (7)
Anakinra	1 (6)	0	13 (87)	12 (17)	0

***:** *n(%),* ***ECG:** Electrocardiogram,* ***ESR:** Erythrocyte sedimentation rate,* ***CRP:** C-reactive protein,* ***ANA:** anti-nuclear antibodies,* ***NSAIDs:** nonsteroidal anti-inflammatory drugs, na not applicable,* ***PPS:** Post pericardiectomy syndrome*

In total, 16 patients had 36 recurrences (mean 2.25±1.05) during follow-up. The main symptom during the relapses was chest pain, similar to that of the first attack. None of the recurrences resulted in constrictive pericarditis. Four patients (25%) had a history of previous cardiac surgery. Two of these patients had atrial septal defect (ASD) surgery, one patient had fallot tetralogy surgery, and one patient had ventricular septal defect (VSD) surgery. The first attack of pericarditis in these patients occurred an average of 6.4 weeks after surgery. All patients underwent genetic testing for autoinflammatory diseases, including MEFV gene sequencing and extended autoinflammatory panels. No pathogenic or likely pathogenic variants were detected, which indicates that none of the patients had Familial Mediterranean Fever (FMF) or other monogenic autoinflammatory syndromes.

Three patients were treated with nonsteroidal anti-inflammatory drugs (NSAIDs) only. NSAID and colchicine were administered to 13 patients. One patient received corticosteroid (methylprednisolone). One patient with frequent relapses was

Table II: Demographic, clinical and laboratory findings of the patients

Patient	Age at first attack (years)	Gender	Final Diagnose	Symptoms	Pericardial Rub	Typical ECG changes	Pericardial effusion (mm)	Pleural effusion	CRP (mg/dl)	ESR (mm/h)	Number of attacks	Attack number under threatment	PPS	Conseguilty
1	13	Male	PPS	CP, BP	Yes	No	No	No	297	48	4	3	Yes	Yes
2	13	Male	RIAP	CP, D, C	No	No	No	No	27.7	40	2	0	No	Yes
3	14	Male	PPS	CP, D	Yes	No	17	No	210	90	1	0	Yes	No
4	13	Male	RIAP	F, CP	No	Yes	No	No	26	32	4	3	No	No
5	12	Girl	RIAP	CP, D	Yes	No	30	Yes	303	59	2	1	No	Yes
6	10	Male	PPS	CP, D, BP	Yes	No	5	Yes	149	34	2	1	Yes	No
7	16	Male	RIAP	F, CP, D, BP	Yes	No	7,5	Yes	84	88	1	0	No	No
8	13	Male	RIAP	F, CP	Yes	No	22	No	116	21	4	5	No	No
9	8	Male	PPS	F, CP, C	Yes	No	No	No	69	43	2	1	Yes	No
10	10	Girl	RIAP	F, CP	No	No	15	Yes	139	14	1	0	No	No
11	17	Male	RIAP	F, CP, C	No	Yes	No	No	106	46	1	0	No	No
12	16	Male	PPS	F, CP	Yes	Yes	17	Yes	195	19	3	2	No	No
13	14	Male	RIAP	CP	Yes	Yes	8	No	72,9	18	2	1	No	No
14	17	Male	RIAP	CP, D	No	No	7	No	195	70	2	1	No	No
15	16	Male	RIAP	F, CP, D, BP	No	Yes	3.5	No	86	84	2	1	No	Yes
16	8	Male	PPS	CP, D	No	No	17	No	171	74	4	2	Yes	No

ECG: *electrocardiogram,* ***ESR:*** *Erythrocyte sedimentation rate,* ***CRP:*** *C-reactive protein,* ***PPS:*** *Post pericardiectomy syndrome,* ***RIAP:*** *recurrent idiopathic acute pericarditis,* ***F:*** *fever,* ***CP:*** *chest pain,* ***D:*** *dispnea,* ***BP:*** *back pain*

diagnosed with refractory pericarditis and received anakinra treatment. A relapse was observed in patient under anakinra treatment, but no relapse was observed after 12 months of anakinra treatment and remission is currently ongoing. The demographic and clinical characteristics of the patients are shown in Table II.

DISCUSSION

In this study, we evaluated clinical findings and treatment of children and adolescents with recurrent pericarditis. To the best of our knowledge, this is the first study on recurrent pericarditis in pediatric patients in Türkiye. There is insufficient data on recurrent pericarditis in children, and the management of the disease is based on the results of studies conducted in adults.

In the CORP 2 study of 240 cases in the adult age group with recurrent pericarditis, fever was seen in 30% and pericardial effusion in 57%, while chest pain was the main symptom in all patients (100%) (14). Additionally, antinuclear antibody positivity was more common in adults. In our study, pericardial effusion was detected in 69.7% of the patients. While fever was observed in 50% of the patients, 18.7% of the patients had serious disease. In addition, serum inflammatory markers were increased in the majority of patients, and pneumonia or pleuritis were accompanied in 31.2% of the patients. In the largest multicenter study conducted in children with recurrent pericarditis to date, 110 patients were reported by Imazo et al (11). Chest pain was the most common presenting symptom in this multicenter cohort. Pericardial effusion was reported in 80% of the patients. Additionally, similar to our study results, serum inflammatory markers were increased in the majority of patients and fever frequently accompanied the disease. Unlike the results of studies conducted in adult patients, pericardial effusion and fever are more common in childhood recurrent pericarditis, inflammatory markers are significantly higher, and pleuritis is more frequently accompanied. Male predominance (14 out of 16 patients; 87.5%) was observed in our cohort. The reason for this male bias remains unclear, but hormonal and immunogenetic mechanisms are likely to contribute. Moreover, viral triggers—particularly Coxsackie and echoviruses—are more common in boys, which may partly explain this distribution. This finding has been reported in other studies but remains an area that warrants further investigation (11,12).

In developed countries approximately 90% of recurrent pericarditis cases are defined as idiopathic or viral (11). However, recently much evidence, including clinical, genetic and therapeutic, has been presented that allows the association of cases of recurrent pericarditis with autoinflammatory disorders (8,15,16). In the present study, genetic analysis was undertaken on a group of patients. However, no instances of familial Mediterranean fever (FMF) or other monogenic

autoinflammatory syndromes were identified. This finding strengthens the hypothesis that recurrent pericarditis in children is a multifactorial autoinflammatory condition with environmental and immunological influences rather than a monogenic hereditary disorder. Recurrent pericarditis in pediatric patients has a clinical course characterized by a dramatic increase in inflammatory markers, sudden fever attacks, sometimes with pleuropulmonary involvement and arthralgia. However, between attacks there are usually symptom-free periods that include complete well-being and complete normalization of inflammatory markers (8,17). This clinical course is quite similar to the clinical features of some autoinflammatory disorders, such as FMF or tumor necrosis factor receptor related periodic syndrome (TRAPS) (18,19). For this reason, clinicians have considered recurrent pericarditis as an autoinflammatory disease and have tended to use anti-inflammatory, immune modulators and immunosuppressive drugs in its management and treatment.

Nonsteroidal anti-inflammatory drugs represent the central component of the therapy; the high dose should be used if tolerated, and given every 8 hours during the acute attack. However, most of the time, the use of NSAIDs alone is not sufficient to prevent recurrences (3, 20). Another well-established treatment is colchicine, which when combined with NSAIDs can improve the response to NSAIDs but also reduce the likelihood of RP recurrence (21,22). In the CORE study (COlchicine for REcurrent Pericarditis), colchicine treatment provided clinical and statistical benefits compared to conventional treatment (23). In this prospective, randomized study, 84 patients with at least one recurrent episode of pericarditis were received either conventional treatment with aspirin alone (group 1) or conventional treatment plus colchicine (group 2). Relapse rates at 18 months were 50.6% in group 1 and 24.0% in group 2. The CORP study (COlchicine for Recurrent Pericarditis), the first prospective, randomized, double-linkage, placebo-controlled, multicenter study in adults, included 120 patients with a first episode of recurrent pericarditis (24). Patients were randomized to receive placebo or colchicine in addition to conventional treatment. The relapse rate was 24% in the colchicine group and 55% in the placebo group. The results of these studies show that colchicine is effective in preventing recurrences when added to conventional treatment. Consistent with these findings, the majority of patients in our cohort received colchicine in combination with NSAIDs, and this approach was associated with effective disease control and a reduced number of recurrences during follow-up We recommend starting colchicine early period of disease and prolonging its use to prevent relapses.

Corticosteroids can be used as triple therapy with NSAIDs and colchicine in patients with refractory disease. Many patients with RP receiving corticosteroid therapy may experience an exacerbation of RP after dose reduction and become completely dependent on corticosteroids to remain asymptomatic. This situation causes significant side effects due to corticosteroid use (17, 25). Imazio et al. (26) demonstrated that corticosteroid use in the treatment of acute pericarditis is an independent risk factor for recurrence. In their study, they compared patients who were received corticosteroids and those who were not. They revealed that pericarditis recurred more frequently compared to other treatments, and that the number of hospitalization increased due to drug-related side effects. Consistent with these observations, corticosteroids were required in only a limited number of patients in our cohort, reflecting their reserved use in refractory cases and supporting a treatment strategy favoring NSAIDs and colchicine as first-line therapy. Therefore, we believe that the use of corticosteroids should not be used except in patients with underlying autoimmune disease and in patients resistant to conventional treatments where new treatment regimens are contraindicated.

Interleukin-1 beta (IL-1β) receptor antagonist (anakinra) appears to be an effective alternative for IRP patients who frequently relapse or develop significant steroid side effects or corticosteroid dependence despite colchicine and anti-inflammatory therapy (27-29). Picco et al. (27) describe a dramatic therapeutic response to anakinra in 3 pediatric patients with steroid-dependent RP. Administration of anakinra in his patients led to resolution of all clinical symptoms and normalization of acute phase reactants. After complete remission, anakinra treatment was stopped and a flare-up of the disease was observed within a few weeks. All symptoms disappeared again by restarting anakinra. No new relapse was observed in any patient during an average follow-up of 6 months. They reported that the use of anakinra could prevent recurrence of the disease (27). Subsequently, Finetti et al. (29) showed that anakinra was effective in preventing recurrences as monotherapy in 15 patients with recurrent pericarditis, 12 of whom were pediatric patients, who were corticosteroid dependent and using colchicine. In accordance with these reports, anakinra was used in a patient with refractory disease in our cohort and was associated with sustained clinical remission during follow-up. If the combination of high-dose NSAIDs and colchicine is insufficient in the treatment, anakinra treatment can be considered instead of corticosteroids as a third-line treatment.

The most reliable biomarker for monitoring pericarditis is CRP. In our cohort, CRP levels were elevated during acute attacks and decreased in parallel with clinical improvement, supporting its reliability for disease monitoring. Normalization of CRP with the disappearance of symptoms is used to monitor patients. Especially, reduction or discontinuation of colchicine or corticosteroids treatment should be based on CRP levels (7).

Limitations:

This study has some limitations inherent to its retrospective, single-center design and the small sample size (n=16), which may limit the statistical power and generalizability of the findings. Additionally, the lack of long-term follow-up data prevents a comprehensive evaluation of late complications,

such as constrictive pericarditis or chronic pericardial effusion. Despite these limitations, our results contribute valuable insight into the clinical characteristics and therapeutic responses of pediatric recurrent pericarditis in a tertiary care setting.

CONCLUSION

Although recurrent pericarditis generally has a good prognosis, the pathogenesis is still unclear. Patients with recurrent pericarditis in childhood have an autoinflammatory phenotype due to fever, elevated acute phase markers, symptom-free periods between attacks, and the presence of pleuritis/arthritis. The fact that IL-1 antagonists are very useful in resistant cases may be encouraging for researchers to conduct new research to understand the pathogenesis of the disease. Furthermore, successful management of patients with recurrent pericarditis requires a teamwork approach involving cardiologists, rheumatologists and clinical immunologists.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Dr. Sami Ulus Hospital Maternity and Child Health and Diseases Training and Research Hospital (16.03.2022, reference number: E-22/03-308).

Contribution of the authors

Manuscript İB, SO, EAA; literature search EAA, SO, EB; study desing EAA, UAÖ,SO, EB; writing İB, EAA, SO, VD, EB. All authors read and approved the final manuscrip

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The authors declare that there is no conflict of interest.

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