Acute rheumatic fever in adult patients

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Abstract

Acute rheumatic fever (ARF) is considered as a disorder of children, and attacks in adults are usually a recurrence of disease acquired in the child’s life. Although the incidence of ARF in children has a decreasing trend in developed countries, resurgent and sporadic epidemics still occur in adults. The first attacks of ARF in adult patients without a childhood history can lead to a diagnostic dilemma.

A medical record review in adults at least 18 years of age with an arthralgia complaint fulfilling 2015 revised Jones criteria was performed from January 1, 2000 to December 31, 2019.

Eleven ARF patients were identified, including 8 with initial attacks (6 females aged 26–42 years, 33.9±5.3) and 3 pre-existing valvular heart disease with recurrent attacks (2 females aged 38–52 years, 45.0±7.0). In addition to febrile pharyngitis and migratory polyarthritis in initial attacks, pericarditis was encountered in 1, valvulitis in 2, prolong PR interval in 3 and skin involvement in 2 patients with erythema marginatum and IgA vasculitis. All responded to antibiotics and nonsteroidal anti-inflammatory drugs therapy with normalized clinical and laboratory abnormalities, no new-onset carditis, and no recurrent disease during a long-term follow-up (3.8–19.8 years, 12.7±5.4).

A sporadic occurrence of adult ARF is observed in southern Taiwan. This disease should be considered by physicians for the differential diagnosis of febrile pharyngitis with arthritis and/or carditis in adults, even in areas with a low incidence of ARF.

Abbreviations: AB = antibiotics, AR = aortic regurgitation, ARF = acute rheumatic fever, ASLO = anti-streptolysin O, AVB = atrioventricular block, C/L = clinical/laboratory, CRP = C-reactive protein, CS = corticosteroids, ECG = echocardiography, EM = erythema marginatum, ESR = erythrocyte sedimentation rate, F/U = follow-up, FA = first attack, FGC = first-generation cephalosporin, GAS = group A streptococcus, MR = mitral regurgitation, MS = mitral stenosis, NA = not available, ND = not done, No = number, NSAIDs = nonsteroidal anti-inflammatory drugs, PE = pericardial effusion, PSRA = post-streptococcal reactive arthritis, RA = recurrent attack, RHD = rheumatic heart disease, SC = Sydenham chorea, SN = subcutaneous nodule, TS = throat swab, UA = urinalysis, VRS = valve replace surgery, US = United States.

Keywords: acute rheumatic fever, adult, febrile pharyngitis, group A streptococcus, migratory polyarthritis, rheumatic heart disease

1. Introduction

A major impact of acute rheumatic fever (ARF), an autoimmune-mediated consequence of group A streptococcus (GAS) infection, is the irreversible damage to cardiac valves due to recurrent attacks, leading to rheumatic heart disease (RHD). Because of better access to medical care and less household overcrowding in developed countries, ARF has a declining incidence at the turn of 20th century. Nevertheless, there have been periodical resurgences, particularly in the United States, with outbreaks in civilian and military populations since the mid-1980s, and the disease remains a public health problem in developing nations.

ARF is considered as a disorder of children, and attacks in adults are usually a recurrence of disease acquired in childhood.

Although initial attacks in the adult life are rarely observed even with a higher incidence in developed countries in the past, resurgent and sporadic epidemics of adult ARF still occur in recent decades. In Taiwan, under adequate microbiological survey on febrile pharyngitis in school children, there are no reported children ARF in southern area since the 1990s. Nevertheless, young women with initial-attack ARF were sporadically identified in this area during the early 2000s, indicating a defective primary prophylaxis of preceding GAS pharyngitis in adults. Presently, owing to a rare occurrence of ARF in developed countries, a first presentation in adults deficient in childhood history can cause a diagnostic dilemma. Since there exists a limited number of reported case series with adult ARF in recent decades, we performed a retrospective study with medical records review under the permission of institutional review board for this rare disease.
2. Methods

2.2. Study population

With the permission of institutional review board (number B-ER-105-108, human study approval on April 28, 2016, with research term amendment extending till April 30, 2025, and patients’ informed consent waived due to the study being classified as a retrospective medical record review), a medical records review was carried out for adults at least 18 years of age with a complaint of arthralgia who visited our hospital from January 1, 2000, to December 31, 2019. All patients who met the 2015 revised Jones criteria for low-risk populations,[7] either initial or recurrent ARF, were enrolled in this study. Major criteria included carditis, polyarthritis, chorea, erythema marginatum and subcutaneous nodule, while minor criteria consist of polyarthralgia, fever (≥38.5°C), elevated erythrocyte sedimentation rates (ESR, ≥ 60 mm/h) or C-reactive protein levels (CRP, ≥30 mg/L), and prolong PR interval (>0.2 second). In addition to the evidence of preceding GAS infection, patients must have 2 major or 1 major/2 minor, and 2 major, 1 major/2 minor or 3 minor manifestations to reach a final diagnosis of initial and recurrent ARF, respectively.

2.3. Data collection

Demographic, clinical, laboratory, imaging, and pathological information were analyzed, including age/sex, clinical manifestations, anti-streptolysin O (ASLO) titers (local population normal reference 116 IU/mL), ESR/CRP, liver function, hemogram, microbiological culture, electrocardiography, echocardiography (ECG), and skin biopsy. A review in medication profiles of antibiotics, corticosteroids (CS), and nonsteroidal anti-inflammatory drugs (NSAIDs) was performed. Data are presented as the mean and standard deviation for continuous variables and as percentages for categorical variables.

3. Results

In this study, 11 patients with ARF were identified, 8 females aged 26 to 52 years (36.9 ±7.5). There were 8 initial-attack cases without previous ARF or RHD, 6 females aged 26 to 42 years (33.9 ±5.3), who met the initial ARF criteria, with 3 major/2 minor, 2 major/3 minor, 1 major/3 minor, and 1 major/2 minor manifestations in 1, 1, 1, and 5, respectively (Table 1). Three patients had GAS re-infection, 2 females aged 38 to 52 years (45.0 ±7.0) with pre-existing RHD including aortic regurgitation (AR)/mitral regurgitation (MR) in 1 and mitral stenosis (MS)/MR in 2. They fulfilled the recurrent ARF criteria with 2 major/2 minor in 1 and 1 major/2 minor manifestations in 2. These patients had no new-onset carditis at the time of diagnosis.

In patients with initial-attack ARF, all presented with high fever and pharyngitis, followed by migratory polyarthritides with

![Table 1](https://example.com/table1.png)

| No. | Age/sex | Clinical presentations† | Articular onset after infection‡ | Cardiac involvement§ | Laboratory presentations‖ | ASLO titers | Throat swab culture | Treatment | Outcome under long-term F/U |
|-----|---------|-------------------------|---------------------------------|----------------------|---------------------------|-------------|---------------------|-----------|---------------------------|
| 1   | 36F     | High fever, sore throat, migratory polyarthritides | Large joints, 1–2 wk | Nil | Elevated CRP/ESR, normocytic anemia | 772 IU/mL | Streptococcus pyogenes | NSAIDs, penicillin | No recurrence or C/L anomaly |
| 2   | 29F     | High fever, sore throat, arms with red macules, migratory polyarthritides | Large joints, 3 wk | AR and PE, prolong PR interval | Elevated CRP/ESR, normocytic anemia | 1460 IU/mL | Nil | NSAIDs, FGC | No recurrence or C/L anomaly |
| 3   | 42F     | High fever, sore throat, migratory polyarthritides | Large and foot small joints, 2 wk | Nil | Elevated CRP/ESR, normocytic anemia | 1520 IU/mL | S pyogenes | NSAIDs, penicillin | No recurrence or C/L anomaly |
| 4   | 26F     | High fever, sore throat, legs with purpura, migratory polyarthritides | Large and hand small joints, 2 wk | MR, prolong PR interval | Elevated CRP/ESR, normocytic anemia, hepatic dysfunction | 2260 IU/mL | Nil | NSAIDs, CS, FGC | No recurrence or C/L anomaly |
| 5   | 39F     | High fever, sore throat, migratory polyarthritides | Large joints, 2–3 wk | Nil | Elevated CRP/ESR | 364 IU/mL | Nil | NSAIDs, FGC | No recurrence or C/L anomaly |
| 6   | 30M     | High fever, sore throat, migratory polyarthritides | Large joints, 2 wk | Nil | Elevated CRP/ESR | 540 IU/mL | S pyogenes | NSAIDs, FGC | No recurrence or C/L anomaly |
| 7   | 35F     | High fever, sore throat, migratory polyarthritides | Large joints, 3–4 wk | Prolong PR interval | Elevated CRP/ESR, normocytic anemia | 861 IU/mL | S pyogenes | NSAIDs, penicillin | No recurrence or C/L anomaly |
| 8   | 34M     | High fever, sore throat, migratory polyarthritides | Large joints, 3 wk | Nil | Elevated CRP/ESR, normocytic anemia, hepatic dysfunction | 1330 IU/mL | Nil | NSAIDs, penicillin | No recurrence or C/L anomaly |
| 9   | 38F     | High fever, sore throat, migratory polyarthritides | Large and foot small joints, 2–3 wk | Pre-existing RHD, MR and MS, no new-onset carditis | Elevated CRP/ESR, normocytic anemia | 605 IU/mL | S pyogenes | NSAIDs, penicillin | No new-onset carditis or recurrence, with VRS |
| 10  | 45F     | Sore throat, polyarthralgia | Large joints, 1–2 wk | Pre-existing RHD, AR and MR, no new-onset carditis | Elevated CRP | 330 IU/mL | Nil | NSAIDs, FGC | No new-onset carditis or recurrence, with VRS |
| 11  | 52M     | Sore throat, polyarthralgia | Large joints, 2 wk | Pre-existing RHD, MR and MS, no new-onset carditis | Elevated CRP | 478 IU/mL | Nil | NSAIDs, FGC | No new-onset carditis or recurrence |

AR = acute rheumatic fever, ARF = acute rheumatic fever, ASLO = anti-streptolysin O, C/L = clinical/laboratory, CRP = C-reactive protein, CS = corticosteroids, ESR = erythrocyte sedimentation rates, F/U = follow-up, FGC = first-generation cephalosporin, MR = mitral regurgitation, MS = mitral stenosis, NSAIDs = nonsteroidal anti-inflammatory drugs, PE = pericardial effusion, RHD = rheumatic heart disease, VRS = valve replace surgery.

*Initial ARF patients (No. 1–8) and recurrent ARF (No. 9–11).
†High fever ≥38.5°C, biopsy results with erythema marginatum (No. 2) and IgA leukocytoclastic vasculitis (No. 4).
‡Large joints including shoulder, elbow, wrist, hip, knee, and ankle.
§Absent prolong PR interval, pericarditis, and valvulitis within 2 wk, 2 and 6 mo of the diagnosis, respectively.
‖ESR ≥60 mm/h and CRP ≥30 mg/L.

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a latency period of 1 to 2 to 3 to 4 weeks (2.6 ± 0.7). Evanescent red polycyclic maculopapular eruptions over arms occurred after the onset of fever in case no. 2 (Fig. 1A), and purpuric rash over legs after the development of arthritis in case no. 4. Skin histopathological findings were compatible with erythema marginatum (Fig. 1B) and IgA leukocytoclastic vasculitis, respectively. Notably, cases no. 2 and 4 had carditis with AR and MR, respectively. A prolong PR interval was also noted in cases no. 2 and 4 as well as 7. There were no heart failure presentations in these patients.

Laboratory examinations revealed increased CRP levels or plus ESR, normocytic anemia, and liver dysfunction in 11, 7, and 2 patients, respectively. Microbiological survey demonstrated elevated ASLO titers in 11, and positive Streptococcus pyogenes cultures in 5 patients. Throat swab cultures performed in household contacts from reported cases failed to yield GAS pathogens. All patients received antibiotics therapy to treat infection and eradicate carriage for at least 10 days. NSAIDs were prescribed with rapid efficacy for curing inflamed joints. In case no. 4, CS were prescribed for 1 week with resolved rash. Despite no specific therapy for cardiac anomaly in cases no. 2, 4, and 7, disappearance of prolong PR interval, pericarditis, and valvulitis were noted within 2 weeks, 2 months, and 6 months of the identification, respectively. All patients had normalized clinical and laboratory abnormalities during follow-up.

Children with an episode of ARF are at a higher risk for recurrent attacks, and secondary antibiotics prophylaxis is recommended to prevent further GAS infection, especially in those with carditis. Our patients received secondary prophylaxis, and there were no recurrences of ARF during a follow-up of 3.8 to 19.8 years (12.7 ± 5.4). New-onset carditis was not observed in cases no. 2, 4, and 7 with an observation period of 5.6 to 18.5 years (12.6 ± 6.5). Despite 2 under valve replace surgeries, there were no further cardiac abnormalities in recurrent-attack cases no. 10, 11, and 12 during a follow-up of 10.6 to 19.8 years (15.2 ± 4.6).

As shown in Table 2, 5 patients, 2 females aged 23 to 35 years (29.6 ± 5.0), with elevated ASLO and CRP levels or plus ESR, presented with additive oligoarthritis in 2 and polyarthritis in 3, involving large joints in 5 and plus small hand joints in 1. Articular onset was no more than 2 weeks after GAS infection. There was no extra-articular or cardiac involvement. There had 1 major/1 minor and 2 patients had 2 minor manifestations, not matching the initial AR criteria but fulfilling the post-streptococcal reactive arthritis (PSRA) diagnosis. All patients received NSAIDs and antibiotics therapy. Despite not under secondary antibiotics prophylaxis, no carditis was identified during their follow-up of 2.1 to 13.6 years (6.5 ± 4.6).

Table 3 shows comparison of our cases with other 4 case series with at least 10 patients published between 1989 and 2019.[3,4,9,10] Except for an US military outbreak,[3] there were predominantly younger female victims. The major criterion of polyarthritis was identified in most cases from all series; however, not all cases presented with a characteristic migratory pattern. Migratory polyarthritis might be masked or modified on usage of the readily available over-the-counter NSAIDs, underlining the need for obtaining an accurate history in suspected patients.[7] Carditis occurrence with valvulitis as the commonest anomaly in first-attack ARF was higher in developing nations than the US (67% vs 33%). There were no new-onset carditis in recurrent-attack ARF from the US series, contradictory to those from developing nations (0% vs 34%). A carditis-related death was found in an African woman,[8] whereas unresolved MR was noted in 3 US navy recruited men.[3] Prolong PR interval was not infrequently detected, ranging from 17% to 41% in different series.

Erythema marginatum, subcutaneous nodule, and Sydenham chorea were rarely observed in all series. Nормocytic anemia and hepatic dysfunction have been demonstrated in the acute stage with transient and asymptomatic nature.[5] All patients received NSAIDs for arthritis therapy and antibiotics for GAS treatment, carriage eradication, and/or secondary prophylaxis. Furthermore, some patients received CS therapy for severe articular and cardiac manifestations. Long-term follow-up in the United States and the present case series revealed neither worsening carditis nor disease recurrence.

### 4. Discussion

Based on higher occurrences of arthritis and carditis, before establishing an ARF diagnosis, differential diagnosis should be considered for articular and cardiac complaints with the help of ECG/electrocardiography examinations and laboratory tests including ASLO, CRP/ESR, and throat swab culture.[7] Notably, PSRA is a distinct entity, distinguished from ARF as a separate disease.[10] It usually begins within 10 days following GAS infection and presents with additive and prolong natures, while ARF-related polyarthritis typically has a longer latency with migratory and transitory characters. In spite of the presence of cardiac involvement in children with PSRA, there is no increased risk of valvular heart disease in adult patients.[3] In our series, 5 patients with additive oligoarthritis/polyarthritis and lacking of extra-articular or cardiac involvement were unable to match the initial ARF criteria. Although pharyngitis is an early manifestation of adult-onset Still’s disease,[11] there is no laboratory evidence of GAS infection. Interestingly, it has been described that children with recent GAS infection were first described to develop IgA vasculitis and rheumatic carditis, followed by...
reported cases of adult ARF with both features, similar to our case no. 4. [12]

ARF predominantly affects the pediatric population, and most adults with this disease have their initial attacks in the child’s life. [2] Although a first episode of this disease is infrequent in adults, absent childhood history cannot exclude an ARF diagnosis in adult patients. The initial presentation of this disorder in adults without a history can lead to diagnostic difficulties. Furthermore, given that there is better completion of secondary prophylaxis and less household overcrowding in recent decades, misdiagnosis can occur in adults with a childhood history and present clinical features mimicking ARF. Notably, in developing countries, ARF predominantly affects the pediatric population, and most adults with this disease have their initial attacks in the child’s life. [2] Although a first episode of this disease is infrequent in adults, absent childhood history cannot exclude an ARF diagnosis in adult patients. 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Notably, in developing
 nations, both initial- and recurrent-attack adult ARF had higher frequencies of new-onset carditis. Nevertheless, in the US, there were a lower occurrence of cardiac anomaly in initial-attack adult patients, and no new-onset carditis in patients with recurrent ARF. Functional properties of surface proteins from GAS have been demonstrated to be correlated with clinical invasiveness. Diverse microbial virulence in different areas might have an impact on cardiac involvement in adult ARF.

In the acute stage of ARF, cardiac inflammation typically presents as valvulitis involving mitral and aortic valves, followed by pericarditis, and rarely myocarditis. Although a traditional diagnosis of rheumatic carditis is by auscultating the valvular lesions, ECG survey has improved the diagnostic accuracy of heart involvement to include subclinical carditis with silent symptoms. All series in Table 2 used ECG to detect valvular and pericardial involvement. Acute myocarditis is a rare complication, and it can be presented with congestive heart failure as reported in a young woman with initial-attack ARF. Although transient first-degree block with prolong PR interval is a not uncommon finding, higher-degree conduction disturbance associated with myocardial injury can also be observed in adult ARF as demonstrated in 3 young men with reversible second-degree or complete heart block.

For initial-attack adult patients in the US, in spite of unresolved MR without cardomegaly or heart failure in 3 young male recruiters from a 10-case military cluster, no adult patients were found to have persistent cardiac squeal in a 53-patient resurgence series. Besides a residual benign MR in a young woman with uneventful pregnancy, there was complete recovery in 3 carditis patients with MR or plus AR from a 12-case resurgent community. In our 11-case series, resolved MR and AR were found in 2 young females within 6 months of the identification. Collectively, these observations indicate a benign course of carditis in initial-attack adult ARF. ARF is the result of host immunological reactions to GAS. No recurrence in adults with first attack naive to ARF in contrast to recurrent attacks in patients with GAS infection during childhood, possibly reflecting the differences in age-dependent immune responses against the streptococcal pathogens. Although there are no controlled long-term studies to address the efficacy of secondary antibiotic prophylaxis in adults with initial-attack ARF, this strategy appears to prevent the development of RHD.

In conclusion, despite being considered as a childhood disorder, a sporadic occurrence of ARF in adults is observed in southern area of Taiwan. This disease should be considered by physicians for the differential diagnosis of febrile pharyngitis with arthritis and/or carditis in adults, even in areas with a low incidence of ARF.

Acknowledgments
The authors are indebted to Prof Hung-Chi Lue, National Taiwan University Children Hospital and Prof Ching-Chaun Liu, National Cheng Kung University Hospital for their valuable comments and viewpoints on ARF in Taiwan.

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