Netherlands
The Journal of Medicine

CASE REPORT

Cardiac failure following group A streptococcal infection with echocardiographically proven pericarditis, still insufficient arguments for acute rheumatic fever: a case report and literature update

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ABSTRACT

We recently encountered a 49-year-old female who developed fever due to group A streptococcal (GAS) bacteriaemia spreading to an abscess in the iliac muscle and a bacterial monarthritis of the right knee with a sterile arthritis of her left knee. Treatment was started with a six-week course of intravenous penicillin. She developed a mitral valve insufficiency and pericarditis on the tenth day of admission. In the third week heart failure developed with, on echocardiograph, a high output left ventricular failure without signs of valvulitis or myocarditis. Using a diuretic regimen she was recompensated. Because of the pericarditis with mitral valve insufficiency corticosteroids were given, which had a rapid beneficial effect. A discussion follows on the position of acute rheumatic fever versus post-streptococcal reactive arthritis in this clinical picture and the literature is updated.

INTRODUCTION

The last decades have witnessed a striking resurgence of sequelae of infections with β-haemolytic streptococci and, in particular, group A streptococci (GAS). GAS infection may lead to both pyogenic and non-purulent sequelae. Classically, a non-purulent migratory polyarthritis secondary to GAS infection is attributed to acute rheumatic fever (ARF).[1] The body of evidence has grown, however, that in the developed world several different poststreptococcal syndromes can be recognised, including poststreptococcal reactive arthritis (PSRA).[2-6] ARF differs from PSRA with regards to clinical characteristics, but also to levels of humoral immunity,[7-9] and to genetics.[10] We describe here a patient who interestingly shows a simultaneous purulent and non-purulent sequel due to GAS; this patient does not meet the Jones criteria for ARF, but more or less fulfils the preliminary criteria for PSRA as proposed by Ayoub and Ahmed.

CASE REPORT

A 49-year-old female was admitted because of high fever and malaise. She recalled generalised malaise for 12 days prior to admission without a sore throat or flu-like symptoms. The last two days before admission she had been feeling cold and shivery. Nobody in her family had been ill recently. Several times a week she looked after two small children in her neighbourhood. Physical examination revealed generalised illness with some pharyngitis and fever of between 38 and 39°C. Her heart appeared normal on percussion and auscultation: no murmurs or symptoms of a pericarditic crepitus were heard. On palpation the left upper abdomen was painful, without a clear palpable tumour. Both knees were arthritic. On puncture 60 ml purulent fluid was drawn from the right knee: the leucocyte count was 30 x 10^9/l, a direct preparation showed Gram positive cocci and culture revealed GAS. Puncture from the left knee produced 40 ml clear synovial fluid with a leucocyte count of <0.1 x 10^9/l, a direct preparation showing no micro-organisms and a

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negative culture. Laboratory investigation revealed the following: ESR 64 mm/hr (normal: <12 mm/hr), CRP 436 mg/l (normal: <10 mg/l), haemoglobin 6.3 mmol/l (normal: 7.2-9.8 mmol/l), leucocyte count 23.6 x 10^9/l (normal: 4.0-11.0 x 10^9/l) with left-shift, serum creatinine 81 µmol/l (normal: <95 µmol/l), ASAT 76 U/l (normal: <45 U/l), ALAT 90 U/l (normal: <45 U/l), alkaline phosphatase 237 U/l (normal: <80 U/l), gamma glutamyltranspeptidase 140 U/l (normal: <100 U/l), IgG type kappa paraprotein 9.4 g/l with residual gamma globulin 7.0 g/l, and normal IgA/IgG/IgM levels, without Bence Jones proteinuria. Serologically she was negative for rheumatoid factor but had an elevated antistreptolysin O (ASO) >3600 U/l (normal: <200 U/l) and antideoxyribonuclease B (anti-DNase B) >1200 U/l (normal: <200 U/l). Bacteriological culture of blood and purulent synovial fluid were positive for GAS, M serotype 11, T serotype 11 with exo-enzymes A and C.

A chest X-ray, abdominal ultrasonography and echocardiography performed on admission were all normal. Abdominal CT scan on the second day after admission showed thickening of her left iliac muscle suggestive of an abscess in statu nascendi. Drainage of this abscess was impossible. Thoracoabdominal CT scan excluded a generalised lymphadenopathy.

It was concluded that the patient had a sterile left-sided gonarthritis, a bacterial right-sided gonarthritis and an incipient iliac abscess, all due to GAS. She also had a monoclonal paraproteinaemia, which was not thought to be a predisposing factor for the aforementioned septic sequelae, as the total gamma globulin level was adequate for normal humoral immunity.

During a six-week period she was treated intravenously with penicillin 24 x 10^6 U/24hrs. On the tenth day of admission echocardiography revealed a pericarditic fluid and a mitral valve insufficiency. Several days later she gradually developed congestive heart failure. During this third week of admission, congestive heart failure progressed, which echocardiographically was primarily characterised by severe dysfunction of the left ventricle.

Recompensation was reached by using intravenous bumetanide. The severe cardiac dysfunction was echocardiographically not proven to be due to a myocarditis, but it cannot be excluded completely; a cardiac biopsy was not performed as it was thought to be a too risky procedure. As echocardiography had revealed a myocardial dysfunction with pericarditis and a secondary mitral valve insufficiency, a diuretic regimen was combined with a course of prednisone 50 mg daily. She made a quick recovery. After six weeks of intravenous penicillin the iliac muscle abscess had vanished and daily intravenous penicillin was switched to an intramuscular depot of 1.2 x 10^6 U benzathine-benzylpenicillin every three weeks (later every four weeks). She was send home eight weeks after admission on prednisone 5 mg a day, in a tapering dose regimen, and benzathine-benzylpenicillin 1.2 x 10^6 U every three and later every four weeks, for a period of two years. During this treatment, the gammopathy resolved (semi)spontaneously within six months: IgG type kappa 9.4 g/l at the beginning, 7.8 g/l after one month, 1.6 g/l after four months and not detectable after six months.

Findings of sequential echocardiography

An echocardiogram on the third day after admission revealed normal left and right ventricular function without further abnormalities. One week later there was a mild mitral valve insufficiency with some pericarditic fluid. Gradually a congestive heart failure developed. Two weeks later echocardiography revealed severe dysfunction of the left ventricle, whereas the right ventricle was functioning nearly normally. There were no symptoms compatible with endocarditis, nor were valvulitis or valvular vegetations found; however, a myocarditic component cannot be excluded completely. Five weeks after admission echography revealed normal cardiac functioning without pericarditic fluid: a complete resolution had occurred.

DISCUSSION

Lancefield GAS account for about 3 to 17% cases of septic arthritis.[11] The number of serious invasive streptococcal infections has increased over the last decade,[12] possibly due to spreading of more virulent clones, higher numbers of patients with conditions interfering with immunity, and/or alterations in patterns of child care. Common routes of entry for GAS are the nasopharynx, surgical wounds and the skin; in many patients, however, the portal of entry cannot be ascertained, as was the case in our patient. Next to pyogenic sequelae, GAS infections are known for their non-pyogenic, sterile but sometimes devastating sequelae such as in ARF. The GAS strains epidemiologically associated with epidemics of ARF tend to belong to a limited number of M serotypes, fail to synthesise the alpha-lipoproteinase known as opacity factor, and are often heavily encapsulated. After several decades of a steadily declining frequency of ARF, the past decades have witnessed a striking resurgence of PSRA in the developed world.[6] Next to bacterial factors, host factors play a role, primarily in an individual's susceptibility for developing PSRA or ARF.

Genetically, there are differences between hosts with ARF and hosts with PSRA. ARF is significantly more associated with HLA DRB1*16, and PSRA with HLA DRB1*01.[10] This may at least partly explain a difference in genetic susceptibility between individuals. Immunologically, ARF is associated with a cellular and humoral overstimulation. A number of B lymphocytic antigens have been associated

with ARF.[7] Most promising is the B lymphocytic stimulation of the allogenic cellular surface marker D8/17. Using a selected cut-off level of reactivity with D8/17 positive B cells, 100% of ARF patients but only 14% of controls are positive.[7] This humoral hyper-responsiveness following streptococcal infection appears to only occur in part of the GAS-infected population. *In vitro* elevated D8/17 binding to B lymphocytes has therefore been proposed as a susceptibility marker for developing ARF.[7,8] In PSRA markers of humoral responsiveness have not yet been studied to our knowledge. A pilot study, which we recently performed in Dutch PSRA patients, revealed elevated D8/17 positive B lymphocytes in a minority (28%) of the PSRA patients, suggesting that most Dutch PSRA patients may lack this major risk factor for serious organ involvement as occurs in ARF.[9] This may be due to an absence of humoral disturbance of B lymphocytic hyper-responsiveness, as has been demonstrated to persist *in vitro* in ARF for at least two years after the initial attack.[13] It then becomes questionable whether long-term penicillin prophylaxis is still merited in all patients with GAS-induced PSRA. A five-year monthly penicillin prophylaxis as indicated in ARF would probably mean overtreatment in PSRA. A two-year prophylactic course of monthly penicillin appears to be sufficient to prevent carditis in PSRA in the Netherlands.[14] Whether prophylaxis with a monthly penicillin course is really needed in GAS-induced PSRA warrants further investigation in a randomised controlled trial.

In the patient presented here, heart failure developed concurrently with an intravenous physiological saline infusion together with a penicillin infusion consisting of an extra 43 mmol sodium, comparable with only 280 ml physiological saline infusion extra a day. There were no echographic symptoms of myocarditis, nor was valvulitis present to explain the heart failure. These cardiac sequelae occurred together with arthritis following an M-type 11 GAS infection, which is a type not known from the ARF literature. Clinically, a migratory polyarthritis,[1] or a myocarditis or valvulitis, would have been essential for a diagnosis of ARF meeting Jones criteria. The patient, however, does not meet the Jones criteria but does fulfil the preliminary criteria of PSRA as proposed by Ayoub and Ahmed (*table 1*).[15]

First attacks of ARF are accompanied by carditis in >30%.[16-19] Moderate to severe carditis is usually an indication for corticosteroids, which are generally thought to be superior to salicylates in rapidly resolving acute manifestations. It is suggested that the incidence of carditis in ARF may be somewhat lower in elderly than in younger patients.[20,21] Nowadays, ARF and PSRA are both known to occur sporadically with pericarditis but they also have some dissimilarities, which may be helpful in categorising a patient (*table 2*). PSRA occurs predominantly in adults, whereas ARF predominates in young children.[22] ARF is almost invariably found between 5 to 20 years of age, with a peak incidence at 8 years, contrary to the PSRA patient group in which the mean age is around 32 to 42 years.[4] The predominant type of arthritis differs: ARF is known for its migratory type of polyarthritis occurring in 50 to 100%,[1,13,23,24] whereas PSRA is known for its non-migratory type of monarthritis, pauciarthritis or polyarthritis. A monarthritic or pauciarticular presentation as in the presented patient appears to be another distinction from ARF.

Table 1

Guidelines for the diagnosis of ARF[1] and proposed criteria for the diagnosis of PSRA[15]

SET OF CRITERIA		SCORE OF PRESENTED PATIENT
Modified Jones criteria for ARF		
Major	Carditis	No valvulitis
	Migratory polyarthritis	No
	Sydenham's chorea	No
	Erythema marginatum	No
	Subcutaneous nodules	No
Minor	Fever	Yes
	Arthralgia	No
	Elevated acute phase reactants	Due to septicaemia?
	Prolonged PR interval	No
Proposed criteria for PSRA		
Arthritis: acute onset		Yes
Arthritis: non-migratory		Yes
Arthritis: protracted/recurrent		Possibly
Arthritis: poor response to salicylates/NSAIDs		Yes
Evidence of antecedent streptococcal infection		Yes
No other major Jones manifestation present		Yes
Not fulfilling modified Jones criteria		Yes

ARF = acute rheumatic fever, PSRA = poststreptococcal reactive arthritis. The presence of two major or one major and two minor manifestations indicates a high probability of ARF, if supported by evidence of preceded Group A streptococcal infection.

Table 2
Overview of major differences between GAS-induced ARF and PSRA

	ARF	PSRA
Bacterial causative trigger		
GAS M serotypes	1,3,5,6,18,19,24	9,28[5]
Genetics		
HLA association[10] DRB1*01	No	Yes
DRB1*16	Yes	No
Humoral immunology		
D8/17 elevation[7]	63-100%[7,8]	29%[9]
Clinical sequelae		
Highest prevalence	Developing world	Developed world
Patient age	Young: 5-20 years[24]	Adult: 16-75 years[2-6]
Carditis risk	>30%[16,20]	±0%[2-6]
Pericarditis	Rare[27]	Rare[27]
Myocarditis/valvulitis	50%[27]	6%[27]
Arthritis	Migratory: 50-100%[16,23,24]	Non-migratory: 95%[2-6]
Erythema nodosum/multiforme	<1-7%[20]	33-52%[4,5]
Hepatitis	Sporadic[23]	7-17%[4,5]
Treatment		
Penicillin prophylaxis	5 years/age>18 years[7,8]	1-2 years[9,26]

From the literature we know that socioeconomic environments differ: ARF is still common in developing parts of the world, whereas PSRA occurs sporadically in developed parts of the world. All these factors plea for categorisation of the present patient into the PSRA group.
PSRA may not only develop secondary to GAS, but also secondary to group C and G streptococci (GCS, GGS).[5,25] Antibiotic prophylaxis is not indicated in PSRA secondary to GCS/GGS: non-group A streptococci (NGAS). Therefore, the more benign NGAS-induced PSRA and GAS-induced PSRA should be differentiated.[4-6] ARF can only occur following infection with GAS, particularly the M serotype 1,3,5,6,18,19 and 24, so-called rheumatogenic serotypes.[6,21] In PSRA, the as yet non-rheumatogenic M serotypes 9 and 28 have been described.[5]
If PSRA is diagnosed secondary to GAS, a two-year period of monthly penicillin prophylaxis is given similar to that used in ARF. Although not proven in a randomised controlled trial, a monthly penicillin prophylaxis appears to be safe;[4-6,14] in GAS-induced PSRA it may therefore be justified to advocate penicillin prophylaxis for a one-year period and then discontinue it if carditis has still not occurred.[26] In ARF penicillin prophylaxis should be continued for a minimum of five years or until the age of 21 years, whichever is longer.[26] Any patient with sequelae due to streptococci should be appropriately categorised into one of the poststreptococcal disorders so that proper advice can be given on penicillin and/or corticosteroids. The presented patient clearly shows the dilemmas of diagnosis and treatment in such cases and underscores the necessity of randomised controlled trials into the treatment options of PSRA patient groups.

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