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Rheumatic Manifestations of Infective Endocarditis in Non-Addicts

A 12-Year Study

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Introduction

Infective endocarditis (IE) is due to a microbial infection of the heart valves or of the endocardium in close proximity to either congenital or acquired cardiac defects. This infection may develop insidiously or abruptly and is associated with a high risk of complications. Patients with IE may present with variable manifestations, and its capacity to mimic other conditions may obscure the outcome in those cases where classic manifestations are not evident (19). Rheumatic manifestations are known to be complications of IE (22). Controversy exists about the incidence of these complications, perhaps due to the small number of series describing the frequency and type of rheumatic manifestations and the absence of uniform criteria used for the diagnosis of IE (6, 24, 29, 35, 38). Also, most studies of rheumatic manifestations in IE have been described from tertiary referral centers, which implicates associated problems of referral bias and uncertainty of denominator population. In addition, rheumatic manifestations in patients with IE may not be directly related to the valve infection. In this regard, although intravenous drug use is a well-defined risk factor for the development of IE, intravenous drug abusers may present with systemic necrotizing vasculitis or, more commonly, musculoskeletal complications without IE (26, 30, 37). Therefore, to investigate further the frequency and spectrum of rheumatic manifestations in patients with IE, we examined the rheumatic manifestations in an unselected population of patients with IE without a previous history of drug use. Patients were diagnosed by strict criteria at the single reference hospital for a defined population in northwestern Spain over a 12-year period.

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Abbreviations used in this article: CV, cutaneous vasculitis; IE, infective endocarditis.

Patients and Methods

We performed a retrospective study of the case records of all patients diagnosed with IE in the Department of Medicine of the Hospital Xeral-Calde (Lugo, Spain) from January 1987 through December 1998. The Hospital Xeral-Calde is the only referral center for a mixed urban and rural (60%) population of almost 250,000 people living in the Lugo region of northwestern Spain. The main characteristics of the Lugo population have been reported elsewhere (12, 14–17). Briefly, the population is relatively static, has its own regional language, and is considered to be descended from Celtic origin (8). During the past 2 decades the population has barely changed. Migratory flows have been relatively low during the past 15 years. Although mortality in the Lugo region is higher than in other parts of Spain, it is due to the older age-groups in Lugo: the population is older in the area of Lugo than in most regions of Spain. In this regard, in 1996 the population contained almost 25% of people older than 65 years of age. All patients with suspected IE were sent to the hospital by general practitioners or they self-referred to the emergency unit.

Inclusion criteria

Patients with IE were retrospectively classified according to the Duke criteria (1, 10). Based on those criteria, patients were included in this study if they had clinically definite IE. The Duke schema for clinical criteria defines 2 major criteria and 6 minor criteria. For a case to be considered clinically definite IE, the following criteria were required: Two major criteria, or 1 major criterion and 3 minor criteria, or 5 minor criteria.

The 2 major criteria are the following:

1) Echocardiographic data disclosing evidence of endocardial involvement if 1 of the following findings was observed: a) echodense masses attached to

valvular leaflets or mural endocardium, or b) periannular abscesses, or c) new dehiscence of a valvular prosthesis.

2) Blood cultures positive for IE: a) if typical microorganisms for IE were found from 2 separate blood cultures (classic IE pathogens such as *Viridans streptococci*, *Streptococcus bovis*. and members of the HACEK group of fastidious Gram-negative rods—*Haemophilus* spp., *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*, or b) positive blood cultures for community-acquired *Staphylococcus aureus* and *Enterococcus faecalis* in the absence of a primary focus, or c) persistently positive blood cultures, defined as the recovery of a microorganism consistent with IE from blood cultures taken more than 12 hours apart, or, all of 3 or most of 4 or more separate blood cultures, with the first and the last drawn at least 1 hour apart.

The 6 minor criteria are the following:

1) Predisposing heart disease or intravenous drug use (as discussed before, in the present study intravenous drug users were excluded).

2) Fever if temperature at diagnosis was 38 °C or greater.

3) Peripheral embolic event considered if 1 of the following vascular phenomena was found: major arterial emboli, septic pulmonary infarcts, mycotic aneurysms, intracranial hemorrhage, conjunctival hemorrhages, or Janeway lesions.

4) Immunologic phenomena such as glomerulonephritis, Osler nodes, Roth spots, and positive rheumatoid factor.

5) Echocardiogram consistent with IE but not fulfilling the major criterion described above.

6) Microbiologic evidence consisting of positive blood culture but not meeting the major criterion described above (excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause IE) or serologic evidence of active infection by an organism consistent with IE, such as a positive serology for Q fever.

To avoid an overestimation of the actual frequency of rheumatic manifestations in IE patients, intravenous drug abusers were excluded. Moreover, cases of IE in which the patients had been diagnosed with other conditions that might cause musculoskeletal manifestations (mainly rheumatic diseases) before the onset of IE were also excluded.

Clinical definitions

We defined the clinical features as follows:

Fever was defined as oral or axillary temperature at diagnosis of 38 °C or greater.

A constitutional syndrome was defined if a patient diagnosed as having IE had asthenia, anorexia, and weight loss of at least 4 kg.

Arthralgia and myalgia complaints are subjective symptoms and may vary in different populations. However, we decided to include patients with only arthralgia and myalgia manifestations into the group of patients with musculoskeletal manifestations of IE if these symptoms were recorded whenever reference had been made to joint or muscle pain without clinically apparent synovitis or inflammatory muscle involvement.

As previously described, peripheral synovitis was documented by the number of peripheral joints with obvious inflammatory signs, tenderness, effusion, or stress pain (pain provoked by gentle stretching at the extremes of joint movement) (17).

Cervical, dorsal, or low back pain was considered present if the patient presented with back pain in the absence of previous back injury or previous episodes of back pain.

Sacroiliitis was defined as unrelieved pain and tenderness provoked with direct percussion over the sacroiliac joint along with changes of the sacroiliac joint observed by plain radiographs or computed tomography scan. Also, a positive radionuclide bone scan with technetium-99m methylene diphosphonate of the symptomatic sacroiliac joint in those patients with clinical manifestations and absence of radiographically apparent lesions was also considered to be positive for sacroiliitis.

Infectious spondylitis (septic discitis) was defined in the case of inflammatory back pain and stiffness along with changes of the spine suggestive of disc lumbar infection confirmed by plain radiographs or computed tomography scan. Also, a positive radionuclide bone scan with technetium-99m methylene diphosphonate was considered sufficient for the diagnosis in those patients with inflammatory back pain without a radiographically apparent lesion.

Septic bursitis was defined by inflammation of a bursa in the presence of positive cultures drawn from blood or from the synovial fluid of the bursa.

A patient was considered to have osteomyelitis if there was infection of a bone supported by radiographic or radionuclide studies and a positive culture from the bone tissue or blood. However, patients with vertebral osteomyelitis following spondylitis were not included in this group.

Cutaneous vasculitis (CV) in the setting of IE was diagnosed by characteristic histologic findings on skin biopsy, such as neutrophilic infiltration, leukocytoclasis, and fibrinoid necrosis into the vessel wall of arterioles, capillaries, and postcapillary venules. As previously reported (11, 16), CV related to bacterial infection was considered if the vasculitis was confirmed by a skin biopsy showing leukocytoclastic vasculitis, no drug intake was registered before the development of skin lesions, and bacteriologic evidence of infection was obtained.

Patients were considered to have a condition suggestive of polymyalgia rheumatica if they met the following criteria: a) aged 50 years or older at the onset of symptoms, b) severe and bilateral pain associated with morning stiffness of at least 30 minutes for more than 1 month in at least 2 of 3 areas: neck, shoulder, and pelvic girdles, c) erythrocyte sedimentation rate (ESR by Westergren method) at the time of diagnosis of 40 mm/hr or higher (19).

Nephropathy was defined according to previous studies (12, 16) as follows: 1) renal manifestations if hematuria (≥5 red blood cells/hpf) and/or proteinuria (>300 mg/24 hr) was present, 2) renal insufficiency was considered if the plasma creatinine concentration was more than 125% the upper limit of normal. Levels of liver enzymes (aspartate aminotransferase, alanine aminotransferase) were considered elevated if values at diagnosis were more than twice the upper limit of normal range. Anemia was consid-

ered if hemoglobin was <12 g/dL. Leukocytosis was defined as a white blood cell count ≥11, 000/mm^3, and thrombocytosis as a platelet count >350, 000/mm^3.

Data collection

Clinical and laboratory data at the time of diagnosis of the patients with IE were extracted from their clinical records according to a specifically designed protocol and stored in a computerized file. Besides demographic features, data on the following items were analyzed: delay to diagnosis from the onset of symptoms, predisposing heart disease or other predisposing conditions such as alcoholism, diabetes mellitus, chronic hepatitis, renal insufficiency, hematologic disorders, recent dental manipulation, pneumonia, or other infections within 1 month before the onset of symptoms. Also, history of intravenous drug use or of previously diagnosed diseases other than IE that might explain the development of rheumatic manifestations was recorded. The following clinical data were reviewed: fever, constitutional syndrome, visceral enlargement, cardiac murmur, skin lesions, and those rheumatic manifestations discussed above. In addition to echocardiographic findings, including the specific valve involved in the IE, routine laboratory studies including full blood count, coagulation, and liver and renal function tests performed at the time of diagnosis were also reviewed. In addition, bacteriologic data including results from blood cultures and, when available, data from other sources such as from cultures from skin or synovial fluid were analyzed. Also, when available, data on rheumatoid factor test (by nephelometry), serum C3 and C4 (by nephelometry), and antinuclear antibodies (by indirect immunofluorescence using Hep2 cells as substrate) were examined.

Statistical analysis

Continuous data were described as mean and standard deviation (mean ± SD), and categorical variables as percentages. Comparisons between 2 categories were made using the Student t test for continuous variables. To analyze categorical data we performed the chi-square test. When the minimum expected value was less than 5, the chi-square test with Yates correction was used. Statistical significance was defined as $p \leq 0.05$. Calculations were performed with the statistical package Stata Intercooled, release 6.0 (Stata Corporation, College Station, TX).

Results

Between January 1987 and December 1998, 100 consecutive patients had 110 episodes of clinically definite IE. Rheumatic manifestations were observed in 46 of the 110 episodes (41.8%).

Epidemiologic features of patients with definite IE and rheumatic manifestations

The main epidemiologic characteristics of patients with IE who suffered rheumatic manifestations are summarized in Table 1. Men outnumbered women. Rheumatic manifestations were common in elderly patients. Risk factors were recorded frequently. A degenerative valve disease was the most common underlying heart disease. The most frequent valve involved was the aortic (43.5%), followed by the mitral valve (30.4%).

TABLE 1. Epidemiologic features of 46 cases with definite infective endocarditis and rheumatic manifestations

Age (yr)	
Mean age ± SD	57.5 ± 17.0
Range	18–88
Median	61
Cases in patients > 65 yr	19/46 (41.3%)
Sex (Male/Female)	35/11
Proportion of men	76.1
Delay to diagnosis (days)	
Mean ± SD	30.4 ± 33.1
Range	1–150
Median	29
Predisposing heart disease	24/46 (52.2%)
Other predisposing conditions*	27/46 (58.7%)

*Other predisposing conditions different from intravenous drug use, such as alcoholism, diabetes mellitus, renal insufficiency, non-Hodgkin lymphoma, acute lymphoblastic leukemia, chronic osteomyelitis, recent dental manipulation, pneumonia or other infections within 1 mo before the onset of symptoms.

Types of rheumatic manifestations

In most cases with rheumatic complications these manifestations were included among the initial symptoms or signs of the disease. However, as previously described, in some patients rheumatic manifestations constituted the presenting manifestations of IE (11, 19). Myalgia was a frequent symptom, found in 17 of 110 cases (15.5%) (Table 2). Arthralgia without arthritis was observed in 11 cases (10%). This was more common in proximal joints and those of lower extremities. Peripheral arthritis was clinically evident in 15 cases (13.6%), and sacroiliitis in 1 patient. Low

TABLE 2. Rheumatic manifestations in 110 cases with definite infective endocarditis

	No. of Cases	(%)
Number of cases	46	(41.8)
Myalgia	17	(15.5)
Arthralgia	11	(10.0)
Peripheral arthritis	15	(13.6)
Arthralgia and peripheral arthritis	6	(5.5)
Septic bursitis*	2	(1.8)
Sacroiliitis	1	(0.9)
Septic discitis	2	(1.8)
Back pain†	21	(19.1)
Cervical	5	(4.5)
Dorsal	6	(5.5)
Lumbar (low back pain)	14	(12.7)
Cutaneous leukocytoclastic vasculitis‡	4	(3.6)
Polymyalgia rheumatica	1	(0.9)

*Both cases had involvement of the trochanteric bursa.

†Four patients complained of well-defined back pain in more than 1 spinal region.

‡A skin biopsy showing leukocytoclastic vasculitis was required for the diagnosis.

back pain was described in 14 cases (12.7%). Dorsal and cervical pain were less common, noted in 6 (5.5%) and 5 (4.5%) cases, respectively. Septic discitis was observed in 2 cases (1.8%), and biopsy-proved cutaneous leukocytoclastic vasculitis was found in 4 cases (3.6%). Also, as previously reported, 2 patients with IE suffered trochanteric bursitis caused by *Staphylococcus aureus* (13), and 1 patient had a condition mimicking polymyalgia rheumatica (19). Moreover, a patient who was not considered in the group of cases with rheumatic manifestations had been diagnosed previously as having chronic osteomyelitis in tarsus, and 2 years later developed IE. No other patients from this series were diagnosed as having osteomyelitis before the diagnosis of IE or during their follow-up.

Main laboratory data in patients with IE and rheumatic manifestations

Thirty of the 46 cases had hemoglobin values lower than 12 g/dL at the time of diagnosis (Table 3). Leukocyte counts higher than 11,000/mm^3 were found in almost 50% of the cases. Platelet counts higher than 350,000/mm^3 were uncommon. Microhematuria was observed in more than 50% of the cases. However, although renal insufficiency was also frequent, 6 of the 19 cases who had elevated levels of plasma creatinine had a history of an underlying renal disease before the onset of the symptoms of IE (see Table 3). Other tests, such as rheumatoid factor, serum levels of C3 and C4, and antinuclear antibodies were generally negative or normal (see Table 3).

Peripheral arthritis and sacroiliitis

Fifteen patients of the 46 cases had peripheral arthritis and 1 had sacroiliitis. Among the 13 patients with peripheral arthritis in whom an arthrocentesis was performed, a positive culture in the synovial fluid was found in 7. The microbiology of patients with IE and positive synovial fluid cultures is shown in Table 4. *Staphylococcus aureus* was the most common germ. In another 6 patients, cultures from synovial fluid were negative. In 2 of these 6 patients with negative culture and without a previous history of rheumatic diseases, the study of the synovial fluid disclosed the presence of crystals of monosodium urate in leukocytes. In the 4 patients with negative synovial fluid culture and in the other 2 in whom arthrocentesis was not performed, the arthritis resolved rapidly following specific antibiotic therapy prescribed according to blood culture results. All patients with positive cultures and those 2 patients with a diagnosis of gout had monoarthritis. However, in 2 of the other 6 patients (4 with negative cultures from the synovial fluid and without crystals and 2 patients in whom arthrocentesis was not performed) oligoarthritis involving 3 joints was observed. Epidemiologic and laboratory data and the joints involved in these cases are summarized in Table 4 and Table 5. The only patient with sacroiliitis, a man in his early twenties, had positive blood cultures for *Enterococcus faecalis*, and following antibiotic therapy with ampicillin and gentamicin he experienced a progressive improvement of the sacroiliac pain. Patients with gout were men (61 years of age in both cases) with arthritis in the first metatarsophalangeal joint and ankle, respectively.

Infectious spondylitis

Septic discitis was observed in 2 men. One of them had cervical and the other dorsal involvement. Blood

TABLE 3. Laboratory findings in 46 cases with definite infective endocarditis and rheumatic manifestations

Finding*	Percentage (no. positive/no. tested)
Leukocytosis	47.8 (22/46)
Anemia	65.2 (30/46)
Thrombocytosis	13.0 (6/46)
Renal manifestations	71.3 (33/46)
Hematuria	58.7 (27/46)
Renal insufficiency†	41.3 (19/46)
Elevated liver enzymes	6.5 (3/46)
Positive rheumatoid factor	35.3 (6/17)
Low C3	10.0 (1/10)
Low C4	40.0 (4/10)
Positive antinuclear antibodies	0.0 (0/15)

*See Methods section for definitions.

†Six patients had renal insufficiency and 3 of them were on hemodialysis before the onset of symptoms.

TABLE 4. Main features of 7 patients with peripheral arthritis and definite infective endocarditis who had positive synovial fluid cultures

Age (yr)	
Mean ± SD	66.3 ± 14.2
Range	36–82
Sex (Male/Female)	3/4
White blood cell count (mm^3)	
Mean ± SD	9,786 ± 2,680
Range	5,900–14,100
Hemoglobin value (g/dL)	
Mean ± SD	11.0 ± 1.8
Range	8.8–13.6
Microhematuria*†	71.4 (5/7)
Arthritis*	
Monoarthritis	100 (7/7)
Oligo and polyarthritis	0 (0/7)
Location	
Shoulder	42.9 (3.7)
Hip	28.6 (2/7)
Knee	28.6 (2/7)
Bacteriologic results*	
Staphylococcus aureus	71.4 (5/7)
Streptococcus agalactiae	14.3 (1/7)
Escherichia coli	14.3 (1/7)

*Values are percentages (no. positive/no. tested).

†Microhematuria: ≥ 5 red blood cells/hpf.

TABLE 5. Main features of 6 patients with peripheral synovitis and definite infective endocarditis who had negative cultures and absence of crystals in the synovial fluid (n = 4) or in whom synovial fluid cultures were not performed (n = 2)

Number of cases	6
Age (yr)	
Mean ± SD	47.3 ± 16.1
Range	25–72
Sex (Male/Female)	6/0
White blood cell count (mm^3)	
Mean ± SD	13,317 ± 6,826
Range	5,200–22,500
Hemoglobin value (g/dL)	
Mean ± SD	11.5 ± 2.2
Range	8.3 ± 14.0
Microhematuria*†	33.3 (2/6)
Arthritis*	
Monoarthritis	66.7 (4/6)
Oligoarthritis (3 joints involved)	33.3 (2/6)
Location	
Shoulder	16.7 (1/6)
Wrist	16.7 (1/6)
Metacarpophalangeal	16.7 (1/6)
Knee	50.0 (3/6)
Ankle	66.7 (4/6)

*Values are percentages (no. positive/no. tested).
†Microhematuria ≥ 5 red blood cells/hpf.

cultures were positive for *Streptococcus bovis* and *Streptococcus mitis*, respectively (Table 6). Clinical improvement was observed following specific antibiotic therapy for each case.

Cutaneous leukocytoclastic vasculitis related to IE

Four men with definite IE presented with purpuric skin lesions. In all of them a leukocytoclastic vasculitis was confirmed by biopsy. Three of them had predisposing conditions (Table 7). None had received drugs before the onset of CV. Although blood cultures were positive in all patients, tissue biopsy cultures were negative in 3 of 4 patients in whom they were performed. The main clinical features of 3 patients have been reported previously (11). Two of the 4 patients met the American College of Rheumatology 1990 classification criteria for hypersensitivity vasculitis (5). The other 2 patients were diagnosed as having mixed cryoglobulinemia according to previously reported criteria (21).

Epidemiologic differences in patients with IE with or without rheumatic manifestations

No significant differences in the age at onset of symptoms, gender, and delay to the diagnosis were observed in patients with IE with or without rheumatic manifestations (Table 8). Regardless of the development of rheumatic manifestations, IE was common in patients older than 60 years with a predisposing heart disease. To our surprise, rheumatic manifestations were more commonly observed in patients from rural areas (see Table 8).

Clinical differences in patients with IE with or without rheumatic manifestations

The presence of rheumatic manifestations did not constitute a characteristic to differentiate clinically patients with such manifestations from those without rheumatic features (Table 9). In patients both with and without rheumatic manifestations, a history of asthenia, anorexia, and weight loss was equally common at the time of diagnosis. Typical signs of IE such as fever and murmur were also common in both groups. Likewise, the location of valvular damage was similar (see Table 9).

Laboratory differences in patients with IE with or without rheumatic manifestations

No differences in blood cell counts were found (Table 10). However, patients with rheumatic manifestations more commonly had microhematuria or low serum levels of complement that might support the presence of an immune complex-mediated process.

Microbiologic blood culture results and differences between patients with IE with or without rheumatic manifestations

Microbiologic differences in blood cultures between cases with or without rheumatic manifestations are described in Table 11. *Staphylococcus aureus* was obtained more commonly from blood cultures in patients with rheumatic manifestations. In contrast, *Streptococcus viridans* and *Streptococcus bovis* were found

TABLE 6. Main features of 2 patients with septic discitis

Case	Age/Sex (yr)	Predisposing Conditions	Location of Discitis	Main Laboratory Findings*	Causal Bacteria
1	23/M	Acute lymphoblastic leukemia and dental manipulation	Dorsal region (D11–D12)	Microhematuria	*Streptococcus mitis*
2	55/M	Alcoholism	Cervical region (C3–C4 and C6–C7)	Anemia	*Streptococcus bovis*

*See Methods section for definitions.

TABLE 7. Main features of 4 patients with cutaneous leukocytoclastic vasculitis (CV) related to infective endocarditis (IE)

Case	Age/Sex (yr)	Predisposing Conditions	Main Clinical Features on Admission	Main Laboratory Findings*	Onset of Episode of CV in Relation to Diagnosis of IE	Causal Bacteria
1	72/M	Diabetes mellitus, prosthetic aortic valve	Low-grade fever,† murmur, palpable purpura	Leukocytosis	4 d before	*Acinetobacter*
2	64/M	Corticosteroid therapy for chronic bronchopathy	Low-grade fever,† murmur, palpable purpura	Leukocytosis, RF+, C4 low, cryoglobulins+, raised serum creatinine, microhematuria	1 mo before	*Fusobacterium avium*
3	21/M	Mitral prolapse	Low-grade fever,† murmur, palpable purpura	Leukocytosis	5 d before	*Enterococcus faecalis*
4	44/M	None	Constitutional syndrome*, fever > 38 °C, murmur, palpable purpura, heart failure	RF+, C4 low, cryoglobulins+, anemia, microhematuria	3 mo before	*Streptococcus bovis*

Abbreviations: RF+: positive rheumatoid factor.
*See Methods section for definitions.
†Low-grade fever: temperature between 37.1 and 37.7 °C.

more commonly in patients without rheumatic features. However, the presence of rheumatic manifestations was not associated with a specific pattern of infection, as microbiologic results in patients with rheumatic manifestations were not statistically different from those in the group without rheumatic manifestations ($p = 0.19$) (see Table 11).

Differences in clinical complications and outcome in patients with IE with or without rheumatic manifestations

Cardiac complications were equally frequent in both groups (Table 12). However, embolic complications were present more commonly in patients with rheumatic manifestations. Despite the greater embolic phenomena, the inpatient mortality rate in cases with rheumatic manifestations was not different from that found in the other group.

Discussion

In this study we attempt to examine the frequency of rheumatic manifestations in an unselected and stable population of patients with IE. We also extend previous reports on musculoskeletal manifestations of this condition and provide the first data on the spectrum of rheumatic manifestations from a cohort of patients collected consecutively over a 12-year period in southern Europe. Moreover, we examine the epidemiologic, clinical, and microbiologic differences between patients with IE who developed rheumatic manifestations and those who did not during a long period of

TABLE 8. Epidemiologic differences in patients with infective endocarditis with or without rheumatic manifestations

	Cases with Rheumatic Manifestations	Cases without Rheumatic Manifestations	p Value
Number of cases	46/110 (41.8%)	64/110 (58.2%)	
Age at time of diagnosis			
Mean age ± SD (yr)	57.5 ± 17.0	60.1 ± 16.7	0.22
Sex (Male/Female)	35/11	54/10	
Proportion of men	76.1	84.4	0.23
Delay to diagnosis*			
Mean ± SD (days)	30.4 ± 33.1	36.1 ± 47.1	0.24
Patients older than 65 yr	19/46 (41.3%)	34/64 (53.1%)	0.22
Patients from rural areas	31/46 (67.4%)	29/64 (45.3%)	0.01
Predisposing heart disease	24/46 (52.2%)	41/64 (64.1%)	0.21
Antibiotic therapy prior to diagnosis	7/46 (15.2%)	14/64 (21.9)	0.38

*From the onset of symptoms until the time of the diagnosis.

TABLE 9. Clinical differences in patients with infective endocarditis with or without rheumatic manifestations

	Cases with Rheumatic Manifestations No. (%)	Cases without Rheumatic Manifestations No. (%)	p Value
Number of cases	46/110 (41.8)	64/110 (58.2)	
Constitutional syndrome*	34/46 (73.9)	44/64 (68.8)	0.56
Fever (temperature >38 °C)	44/46 (95.7)	62/64 (96.9)	0.74
Murmur	39/46 (84.8)	59/64 (92.2)	0.22
Splenomegaly	10/46 (21.7)	10/64 (15.6))	0.41
Petechiae	6/46 (13.0)	5/64 (7.8)	0.37
Valve involvement			0.63
Aortic	20/46 (43.5)	28/64 (43.8)	0.86
Mitral	14/46 (30.4)	14/64 (21.9)	0.36
Mitro-aortic	11/46 (23.9)	19/64 (29.7)	0.44
Polyvalvular with tricuspid involvement	1/46 (2.2)	1/64 (1.6)	0.81

*Constitutional syndrome: asthenia, anorexia, and weight loss of at least 4 kg.

time. Of note, the present study provides the first analysis of rheumatic manifestations in IE using the Duke criteria. The use of these criteria allowed us to examine such complications in those patients who fulfilled definite clinical criteria for IE.

At the end of the nineteenth and the beginning of the twentieth century, Osler described IE as a disease that may present variable symptoms and clinical findings (31–33). However, in most studies of IE performed during the next 50–60 years, rheumatic manifestations in IE were not fully documented and were sometimes omitted (2, 23). Indeed, it was not until the 1970s that Deshayes et al (9) drew attention to the importance of musculoskeletal manifestations in IE. Also in the late 1970s, Meyers and Commerford (29) in South Africa and the group of Hunder and colleagues (6) at the Mayo Clinic reported the presence of rheumatic manifestations in 50 of 180 patients and in 84 of 192 cases with IE, respectively. Since then, musculoskeletal manifestations of IE have also been reported in a few series from very different and distant countries such as Israel, France, and Australia (24, 35, 38).

A matter of concern for the clinician who often sees patients with IE is that in most of the series previously reported, echocardiographic abnormalities were not uniformly required for the diagnosis of IE, which in a certain way might alter the actual frequency of rheumatic manifestation in IE. To avoid overdiagnosis of both IE and its associated rheumatic manifestations, we have used the Duke criteria, in which evidence of endocardial involvement remains a major criterion. In addition, in our series either evidence of endocardial involvement as a major criterion or an abnormal echocardiogram consistent with IE but not fulfilling the major criterion described above was found in all cases.

In most studies the frequency of rheumatic manifestations of IE has ranged between 25% and 30% (24, 29, 35, 38). In our series we observed a frequency of 41.8%. The higher incidence in the patients in Lugo may be due to the absence of previous selection of patients attending the hospital and to the inclusion of other rheumatic diseases that had been poorly documented in former studies of IE (24, 29, 35, 38). In this regard, although polymyalgia rheumatica manifestations have been described in patients with IE (4, 18, 19), the presence of this syndrome has not been well documented in former reports. Likewise, cutaneous leukocytoclastic vasculitis has been reported to be associated with infectious agents (11, 25, 27), but no well-defined cases of small-sized biopsy-proved leukocytoclastic CV in IE have been described in those series reported before.

Of note, the frequency of rheumatic manifestations in Lugo patients with IE was similar to that reported from the Mayo Clinic (6). A possible explanation for this coincidence might be the frequent evaluation by

TABLE 10. Laboratory differences in patients with infective endocarditis with or without rheumatic manifestations*

	Cases with Rheumatic Manifestations	Cases without Rheumatic Manifestations	p Value
Number of cases	46/110 (41.8%)	64/110 (58.2%)	
Leukocytosis	47.8 (22/46)	48.4 (31/64)	0.95
Anemia	65.2 (30/46)	70.3 (45/64)	0.57
Thrombocytosis	13.0 (6/46)	14.1 (9/64)	0.88
Microhematuria	58.7 (27/46)	26.6 (17/64)	0.001
Positive rheumatoid factor	35.3 (6/17)	37.5 (6/16)	0.89
Low C3 and/or low C4	40.0 (4/10)	0.0 (0/5)	0.10

*Values are percentages (no. positive/no. tested). See Methods section for definitions.

TABLE 11. Microbiologic blood culture results and differences between cases with infective endocarditis with or without rheumatic manifestations*

	Cases with Rheumatic Manifestations No. (%)	Cases without Rheumatic Manifestations No. (%)
Number of Cases	46/110 (41.8)	64/110 (58.2)
Streptococcus viridans	8/46 (17.4)	20/64 (31.3)
Staphylococcus aureus	15/46 (32.6)	12/64 (18.7)
Streptococcus bovis	5/46 (10.8)	12/64 (18.7)
Staphylococcus epidermidis	3/46 (6.5)	5/64 (7.8)
Enterococcus faecalis	2/46 (4.3)	1/64 (1.5)
Gram-negative bacillus†	4/46 (8.6)	2/64 (3.1)
Polymicrobial‡	2/46 (4.3)	0/64 (0.0)
Other§	5/46 (10.8)	6/64 (9.4)
Number of cases with negative cultures	2/46 (4.3)	6/64 (9.4)

*Microbiologic blood culture results between the group of patients with and without rheumatic manifestations were compared assuming that microorganisms were multinomially distributed: no statistically significant differences were found.

†*Escherichia coli* (2 cases), *Proteus mirabilis*, *Fusobacterium avium*, *Haemophilus parainfluenzae*, *Eikenella corrodens.*

‡*Staphylococcus aureus* and *Streptococcus pneumoniae* (1 case) and *Staphylococcus aureus* and beta-hemolytic streptococcus (1 case).

§Including 1 case of fungal endocarditis caused by *Candida parasilosis.*

rheumatologists in both centers of cases where rheumatic manifestations were suspected. Indeed, by recalculating the incidence of musculoskeletal manifestations in patients with IE from the data reported by the group of Hunder at the Mayo Clinic, it is evident that the frequency of arthralgia, myalgia, peripheral synovitis, low back pain, and septic discitis is strikingly similar in Rochester, Minnesota, and Lugo, Spain. In this regard, in patients from Rochester, Minnesota, arthralgia and myalgia were found in 32 (16.7%) and 27 (14.1%) patients from the total group of 192 patients with IE (6), while in Lugo the proportion of arthralgia and myalgia was 15.5% in both cases. Likewise, peripheral arthritis, septic discitis, and low back pain in the Mayo study occurred in 13.5%, 2.6%, and 9.8% of the 192 patients with IE, respectively. In the present series from Lugo, peripheral arthritis was found in 15 of 110 cases (13.6%), disc space infection in 1.8%, and low back pain in 12.7% (see Table 2).

We compared the epidemiologic and clinical findings of IE cases with rheumatic manifestations in the present study with other studies from other geographic regions (Table 13). We found that rheumatic manifestations in patients with IE from western countries are more common in men aged in the late 40s or 50s, while in Africa and the Middle East the rheumatic manifestations of IE occur in younger people without a predominance in men (6, 9, 24, 29, 35, 38). Periph-

TABLE 12. Differences in clinical complications and in-hospital mortality rate in patients with infective endocarditis with or without rheumatic manifestations

	Cases with Rheumatic Manifestations No. (%)	Cases without Rheumatic Manifestations No. (%)	p Value
Number of cases	46/110 (41.8)	64/110 (58.2)	
Cardiac complications			
Heart failure	15/46 (32.6)	21/64 (32.8)	0.98
Tachyarrhythmia	4/46 (8.7)	7/64 (10.9)	0.70
Conduction disturbance	3/46 (6.5)	6/64 (9.4)	0.59
Pericarditis	1/46 (2.2)	3/64 (4.7)	0.49
Noncardiac complications			
Septic embolism	34/46 (73.9)	25/64 (39.1)	<0.001
Cerebrovascular accident	12/46 (26.1)	10/64 (15.6)	0.18
Disseminated intravascular coagulation	1/46 (2.2)	3/64 (4.7)	0.49
Meningitis	1/46 (2.2)	4/64 (6.3)	0.31
Number of deaths	8/46 (17.4)	18/64 (28.1)	0.19
Cause of death			
Heart failure	3/46 (6.5)	6/64 (9.3)	
Septicemia	3/46 (6.5)	5/64 (7.8)	
Cerebrovascular accident	1/46 (2.2)	2/64 (3.1)	
Sudden death	1/46 (2.2)	2/64 (3.1)	
Other	0/46 (0.0)	3/64 (4.7)	

TABLE 13. Epidemiologic and clinical findings in infective endocarditis cases with rheumatic manifestations, present report and previous studies*

	Lugo Present Spain Report	Rochester, MN USA	Cape Town South Africa	Rouen France	Jerusalem Israel	Bedford Park Australia	Poitiers France
Number of cases	46/110 (42%)	84/192 (44%)	50/180 (28%)	17/64 (27%)	23/91 (25%)	22/93 (25%)	32/108 (30%)
Mean age (yr)	58	49	32	>50	38	NA	NA
Proportion of men	76%	66%	46%	82%	35%	NA	NA
Arthralgia†	16%	17%	11%	6%	19%	2%	16%
Arthritis†	14%	14%	8%	11%	6%	9%	7%
Myalgia†	16%	14%	11%	6%	12%	NA	5%
Low back pain†	13%	10%	8%	9%	11%	12%	7%
Septic discitis†	2%	3%	1%	NA	NA	2%	4%

Abbreviations: NA = not available.
*References 6, 9, 24, 29, 35, 38.
†By recalculating the frequency of rheumatic manifestations in the whole series of patients with infective endocarditis.

eral synovitis and low back pain may be possible warning signs for the presence of IE, as they were uniformly observed in 6%–14% and 7%–13% of the cases, respectively.

An important difference between the present study and those previously reported is the data we present on microbiologic results from the synovial fluid in all but 2 of the 15 patients with IE and peripheral arthritis. In the present series from Lugo, the arthritis in patients with IE and positive synovial fluid cultures was monoarticular (see Table 4). In addition, in keeping with the data from the group of the Mayo Clinic (6) and from Meyers et al (29), in patients from Lugo with peripheral arthritis without positive cultures in the synovial fluid, the peripheral arthritis was mainly limited to a single joint, and the ankle and the knee were the most commonly involved joints (see Table 5).

Regrettably, in the present study we were not able to find specific symptoms or clinical signs that might help to distinguish clinically patients with rheumatic manifestations from those without (see Table 9). However, with respect to the laboratory data, we observed that microhematuria was more common in patients with rheumatic complications (see Table 10). Among the other laboratory data, there was a trend to lower serum complement levels in patients with rheumatic manifestations. These differences in the laboratory tests may be due to an immune complex-mediated process initiated by antigen products of the infectious agent responsible for the IE, or may result from abnormal immunoregulation related to the infectious disease. This fact may be more evident in those cases with IE and leukocytoclastic CV. In this study the incidence of positive serum rheumatoid factor was similar to that reported in earlier reports (6, 36). However, we did not find differences in the incidence of positive rheumatoid factor between patients with or without rheumatic manifestations. In this regard, the presence of positive rheumatoid factor in serum has been correlated specifically with a duration of disease symptoms longer than 6 weeks (6, 28, 34). Due to this, we examined the disease duration in those patients from Lugo in whom serum rheumatoid factor had been tested. In agreement with former reports and regardless of the development of rheumatic manifestations, patients with IE who had a positive rheumatoid factor had a longer disease duration. This difference was statistically significant in those patients with rheumatic manifestations (patients with positive rheumatoid factor, 73.3 ± 29.3 days; median, 67.5 days versus 39.2 ± 43.3 days; median, 30.0 days in those with negative rheumatoid factor; $p = 0.05$). Finally, unlike former reports that described positive antinuclear antibodies in a few patients with IE (6, 7, 34), none of the 15 patients with rheumatic manifestations in whom antinuclear antibodies were tested had positive results.

An important point of interest in the present study was the search for a possible specific pattern of microbiologic infection in those patients with rheumatic manifestations. However, the analysis of blood culture results did not disclose significant differences between patients with or without rheumatic manifestations (see Table 12). Similar results were observed by Thomas et al (38). These authors compared causal pathogens and found no significant differences except for *Streptococcus D*, which was obtained more commonly from blood cultures in patients with rheumatic manifestations. Also, the spectrum of bacterial organisms obtained from the blood cultures in Lugo patients was similar to that described in earlier reports (6, 38). In this regard, streptococci and staphylococci were among the most common bacterial pathogens of IE. In our series 2 patients had septic discitis, and in 1 of them disc involvement occurred in more than 1 discal space (see Table 6). This fact is uncommon but it has been described previously in a few cases of septic discitis in the setting of IE (3, 38).

Another important matter was to examine whether the presence of rheumatic manifestations was associated with a different spectrum of clinical complications and whether these patients had a different outcome from the rest of IE patients without rheumatic complications. The comparison of complications did not yield differences in the cardiac complications

between patients with and without rheumatic manifestations (see Table 12). However, septic embolisms were significantly more common in the cases with rheumatic manifestations. It is also known that renal dysfunction is not infrequent during the course of IE, and may worsen the prognosis of the disease (20). However, although in the present series microhematuria was significantly more common in patients with rheumatic manifestations (see Table 10), no differences in the clinical outcome were found, and the inhospital mortality rate in patients with rheumatic manifestations was not significantly different from that of patients without these manifestations (see Table 12).

In conclusion, the present study supports the claim that rheumatic complications are frequent in patients with clinically definite IE from southern Europe. The presence of musculoskeletal or vasculitic manifestations may be of some help, as warning signs, for the recognition of patients with severe disease who require a rapid diagnosis and therapy.

Summary

Infective endocarditis (IE) is due to a microbial infection of the heart valves or of the endocardium in close proximity to either congenital or acquired cardiac defects. This infection is associated with a high risk of complications. Rheumatic manifestations are known to be frequent complications of IE. Controversy, however, frequently exists about the actual incidence of these complications. This may be due to the small number of series describing the frequency and type of rheumatic manifestations, the absence of uniform criteria used for the diagnosis of IE, and the fact that some studies on rheumatic manifestations in IE have been described from tertiary referral centers, which implicates associated problems of referral bias and uncertainty of denominator population.

To investigate further the incidence, clinical spectrum, and outcome of patients with IE and rheumatic manifestations, we examined the features of patients diagnosed with clinically definite IE according to the Duke classification criteria at the single reference hospital for a defined population in northwestern Spain during a 12-year period. Between 1987 and 1998, 100 consecutive patients had 110 episodes of clinically definite IE. Rheumatic manifestations were observed in 46 of the 110 episodes (41.8%). As in other western countries, they occurred more commonly in men aged in their 50s. The most frequent valve involved was the aortic (43.5%) followed by the mitral valve (30.4%). Myalgia was a frequent symptom. Peripheral arthritis, generally as monoarthritis, was clinically evident in 15 cases (13.6%), and sacroiliitis in 1 patient. Low back pain was described in 14 cases (12.7%). Septic discitis was observed in 2 cases, and biopsy-proved cutaneous leukocytoclastic vasculitis was found in 4 cases. Other conditions such as trochanteric bursitis and polymyalgia were observed in 2 and 1 case, respectively. Apart from a significantly higher frequency of hematuria and a trend to lower serum complement levels in patients with rheumatic complications, no differences in clinical features, laboratory tests, or microbiologic blood culture results were found between cases with IE with or without rheumatic manifestations. Also, although patients with rheumatic manifestations had more embolic complications, the inhospital mortality rate in patients with rheumatic manifestations was not significantly different from that of the rest of the patients. The present study supports the claim that rheumatic complications are frequent in patients with clinically definite IE from southern Europe. The presence of musculoskeletal or vasculitic manifestations may be of some help, as warning signs, for the recognition of patients with severe disease who require rapid diagnosis and therapy.

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References

1. Bayer AS. Revised diagnostic criteria for infective endocarditis. Cardiol Clin 14: 345–50, 1996.
2. Blumenthal S, Griffiths SP, Morgan BC. Bacterial endocarditis in children with heart disease: A review based on the literature and experience with 58 cases. Pediatrics 26: 993–1017, 1960.
3. Boutelier D, Thomas M, Druet P, Vallin J, Dupuy R. Endocardite d'Osler a enterocque revelee par une osteoarthrite vertebrale. Ann Med Interne (Paris) 120: 855, 1969.
4. Brooks RC, McGee SR. Diagnostic dilemmas in polymyalgia rheumatica. Arch Intern Med 157: 162–68, 1997.
5. Calabrese LH, Michel BA, Bloch DA, Arend WP, Edworthy SM, Fauci AS, Fries JF, Hunder GG, Leavitt RY, Lightfoot RW Jr, Masi AT, McShane DJ, Mills JA, Stevens MB, Wallace SL, Zvaifler NJ. The American College of Rheumatology 1990 criteria for the classification of hypersensitivity vasculitis. Arthritis Rheum 33: 1108–13, 1990.
6. Churchill MA, Geraci HJE, Hunder GG. Musculoskeletal manifestations of bacterial endocarditis. Ann Intern Med 87: 754–59, 1977.
7. Cordeiro A, Costa H, Laginha F. Immunologic phase of subacute bacterial endocarditis: A new concept and general considerations. Am J Cardiol 16: 477–81, 1965.
8. Dababneh A, Gonzalez-Gay MA, Garcia-Porrua C, Hajeer A, Thomson W, Ollier W. Giant cell arteritis and polymyalgia rheumatica can be differentiated by distinct patterns of HLA class II association. J Rheumatol 25: 2140–45, 1998.
9. Deshayes P, Durand JP, Houdent G, Humber G, Breton G. A propos des manifestations rhumatologique des endocarditis bacteriens. Rev Rhum 41: 135–39, 1974.

10. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: Utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med 96: 200–209, 1994.
11. Garcia-Porrua C, Gonzalez-Gay MA. Bacterial infection presenting as cutaneous vasculitis in adults. Clin Exp Rheumatol 17: 471–73, 1999.
12. Garcia-Porrua C, Gonzalez-Gay MA. Comparative clinical and epidemiological study of hypersensitivity vasculitis versus Henoch-Schonlein purpura in adults. Semin Arthritis Rheum 28: 404–12, 1999.
13. Garcia-Porrua C, Gonzalez-Gay MA, Ibanez D, Garcia-Pais MJ. The clinical spectrum of severe septic bursitis in northwestern Spain: A 10 year study. J Rheumatol 26: 663–67, 1999.
14. Garcia-Porrua C, Gonzalez-Gay MA, Vazquez-Caruncho M, Lopez-Lazaro L, Lueiro M, Fernandez ML, Alvarez-Ferreira ML, Pujol RM. Erythema nodosum: Etiologic and predictive factors in a defined population. Arthritis Rheum 43: 584–92, 2000.
15. Gonzalez-Gay MA, Alonso MD, Aguero JJ, Bal M, Fernandez-Camblor B, Sanchez-Andrade A. Temporal arteritis in a northwestern area of Spain: Study of 57 biopsy proven patients. J Rheumatol 19: 277–80, 1992.
16. Gonzalez-Gay MA, Garcia-Porrua C. Systemic vasculitis in adults in northwestern Spain, 1988–1997: Clinical and epidemiologic aspects. Medicine (Baltimore) 78: 292–308, 1999.
17. Gonzalez-Gay MA, Garcia-Porrua C, Ibanez D, Garcia-Pais MJ. Osteoarticular complications of Brucellosis in an Atlantic area of Spain. J Rheumatol 26: 141–45, 1999.
18. Gonzalez-Gay MA, Garcia-Porrua C, Salvarani C, Hunder GG. Diagnostic approach in a patient presenting with polymyalgia. Clin Exp Rheumatol 17: 276–78, 1999.
19. Gonzalez-Gay MA, Garcia-Porrua C, Salvarani C, Olivieri I, Hunder GG. The spectrum of conditions mimicking polymyalgia rheumatica in a defined region of northwestern Spain. J Rheumatol 27: 2179–84, 2000.
20. Gonzalez-Juanatey JR, Garcia-Acuna JM, Garcia-Bengoechea J, Rubio J, Duran D, Sierra J, Fernandez-Vazquez F, Gil M. Endocarditis with pericardial bioprostheses: Clinico-pathologic characteristics, immediate and longterm prognosis. J Heart Valve Dis 3: 172–78, 1994.
21. Gorevic PD, Kassab HJ, Levo Y, Kohn R, Meltzer M, Prose P, Franklin EC. Mixed cryoglobulinemia: Clinical aspects and long-term follow up of 40 patients. Am J Med 69: 287–308, 1980.
22. Ho G Jr. Bacterial arthritis. Curr Opin Rheumatol 5: 449–53, 1993.
23. Lerner PL, Weinstein L. Infective endocarditis in the antibiotic era. N Engl J Med 274: 199–206; 259–66; 323–31; 388–93, 1966.
24. Levo Y, Nashif M. Musculoskeletal manifestations of bacterial endocarditis. Clin Exp Rheumatol 1: 49–52, 1983.
25. Lie JT. Vasculitis associated with infectious agents. Curr Opin Rheumatol 8: 26–29, 1996.
26. Lovy MR, Starkebaum G, Uberoid S. Hepatitis C infection presenting with rheumatic manifestations: A mimic of rheumatoid arthritis. J Rheumatol 23: 979–83, 1996.
27. Mandell BF, Calabrese LH. Infections in systemic vasculitis. Curr Opin Rheumatol 10: 51–57, 1998.
28. Messner RP, Laxdal T, Quie PG, Williams RC Jr. Rheumatoid factor in subacute bacterial endocarditis-bacterium: Duration of disease or genetic predisposition? Ann Intern Med 68: 746–56, 1968.
29. Meyers OL, Commerford PJ. Musculoskeletal manifestations of bacterial endocarditis. Ann Rheum Dis 36: 517–19, 1977.
30. Monteagudo I, Rivera J, Lopez-Longo J, Cosin J, Garcia-Monforte A, Carreno L. AIDS and rheumatic manifestations in patients addicted to drugs. J Rheumatol 18: 1038–41, 1991.
31. Osler W. The Gulstonian lectures on malignant endocarditis. Lancet 1: 415–18; 459–64; 505–8, 1885.
32. Osler W. The chronic intermittent fever of endocarditis. Practitioner 50: 181–90, 1893.
33. Osler W. Chronic infectious endocarditis. Q J Med 2: 219–30, 1909.
34. Perez GO, Rothfield N, Williams RC. Immune-complex nephritis in bacterial endocarditis. Arch Intern Med 136: 334–36, 1976.
35. Roberts-Tomson PJ, Rischmueller M, Kwiatek RA, Soden M, Ahern MJ, Hill WR, Geddes RA. Rheumatic manifestations of infective endocarditis. Rheumatol Int 12: 61–63, 1992.
36. Sheagren JN, Tuazon CU, Griffin C, Padmore N. Rheumatoid factor in acute bacterial endocarditis. Arthritis Rheum 19: 887–90, 1976.
37. Simms RW, Zerbini CA, Ferrante N, Anthony J, Felson DT, Craven DE. Fibromyalgia syndrome in patients infected with human immunodeficiency virus. The Boston City Hospital Clinical AIDS Team. Am J Med 92: 368–74, 1992.
38. Thomas P, Allal J, Bontoux D, Rossi F, Poupet JY, Petitalot JP, Becq-Giraudon B. Rheumatological manifestations of infective endocarditis. Ann Rheum Dis 43: 716–20, 1984.