# Infective endocarditis – why should rheumatologists be aware?

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ACTA REUMATOL PORT. 2021;46:77-81


## ABSTRACT

Infective endocarditis has a wide range of clinical manifestations, making the diagnosis complex. Musculoskeletal symptoms whose prevalence is not negligible are often underestimated. This clinical case is about a 44-year-old female patient with previous aortic and mitral valvuloplasty for rheumatic fever valve disease referred to the outpatient Rheumatology department for the migratory onset of pain and swelling of the left lateral malleolus, right wrist, right first finger and left fifth distal phalanx associated with painful punctate lesions of the digital pulps and lateral edge of the feet and migratory and painful erythematous papules lasting for three months. The susceptibility for IE combined with the finding of spleen infarcts, Osler's nodes and a microorganism from HACEK group on blood cultures supported the diagnosis of subacute infectious endocarditis. Other diagnoses were ruled out. The patient was treated with intravenous antibiotic therapy with complete resolution. This case aims to illustrate the difficulty in diagnosing subacute infective endocarditis, the importance of multidisciplinary work and to briefly review the musculoskeletal manifestations of infective endocarditis described in the literature.


**Keywords:** Musculoskeletal manifestations; Infections; Arthritis; Arthralgia; Dactylitis.

## INTRODUCTION

Infective endocarditis (IE) consists of an infection that affects the heart valves and/or the endocardium and is a potentially fatal disease[1,2]. Its diagnosis can be challenging since it can have a wide range of clinical manifestations and an acute, subacute or chronic courses[1,3]. Fever is the most common sign followed by heart murmur. However patients may present with several non-specific symptoms that may mimic other diseases which may delay the diagnosis and proper treatment. It is important to have a high level of suspicion especially in patients with risk factors for IE, such as the presence of a prosthetic valve, history of previous IE or untreated cyanotic congenital heart disease[1].

We report the case of a patient referred to our outpatient rheumatology department suspected of having a rheumatic disease but whose final diagnosis was IE presenting musculoskeletal manifestations.

## CASE REPORT

A 44-year-old female was referred to our outpatient Rheumatology department for inflammatory arthralgias. She had a history of rheumatic fever during childhood with subsequent rheumatic heart disease, which required valve replacement with aortic and mitral mechanical prosthetic valves. She was chronically medicated with carvedilol, perindopril and warfarin.

In the last month, she was having migratory complains that included pain and swelling of the left lateral malleolus, right wrist, right first finger and left fifth distal phalanx; painful punctate lesions of the digital pulps and lateral edge of the feet and migratory and painful erythematous papules. She also reported increased sudoresis but denied weight loss, fever or symptoms suggestive of a connective tissue disorder. The physical examination was unspecific, showing oedema and flushing of the distal phalanx of the 5$^{th}$ left finger, swelling of the left external malleolus and small violaceous puncture lesions on the feet. No cardiac bruit was detected. Since she was hypocoagulated, she was symptomatically treated with topical anti-inflammatory and a short course of deflazacort with progressive weaning. A workup study and a photographic record of the migratory lesions were asked to the pa-

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tient. She brought pictures showing swelling of the right wrist suggesting arthritis as she also reported loss of mobility (Figure 1), dactylitis of the right first finger (Figure 2), lesions suggestive of Osler's nodules (Figure 3) and small migratory and painful erythematous papules (Figure 4).

The blood tests revealed elevation of inflammatory parameters (erythrocyte sedimentation rate of 92 mm/h and C-reactive protein of 7.27 mg/dL), presence of antinuclear antibodies with a titer of 1:160, a speckled pattern and a negative immunoblot, negative rheumatoid factor (RF) and anti-citrullinated protein antibodies, normal levels of angiotensin converting enzyme and negative Borrelia and Coxiella serologies, syphilis and viral markers (HIV, HBV and HCV). Hands and feet x-ray showed osteoarthritis. The study was complemented to exclude an infectious, vasculitic and paraneoplastic disease. The thoraco-abdominopelvic CT scan was requested and showed a nodular enhancement focus of about 10 mm, centered on the mucosa of the lingual face of the right valecule, a solid thyroid nodule of about 30 mm and splenomegaly with areas of hypoperfusion at the periphery of the spleen, in wedge, suggesting outbreaks of infarction. Transoesophageal echocardiography (TOE) showed no unambiguous images of prosthetic or native valve structures vegetation, but it was isolated a microorganism of the HACEK group (Aggregatibacter actinomycetemcomitans) in the blood cultures. The case was discussed with the Infectious Diseases department and the diagnosis of subacute infectious endocarditis was assumed, 3 months after the beginning of the complaints.

The patient was hospitalized and treated with intravenous ceftriaxone 2g for 6 weeks. During hospitalization the CT abnormalities were clarified: thyroid biopsy revealed a follicular lesion of undetermined significance and the otorhinolaryngology examination excluded an oropharyngeal neoplasm. A dental evalua-

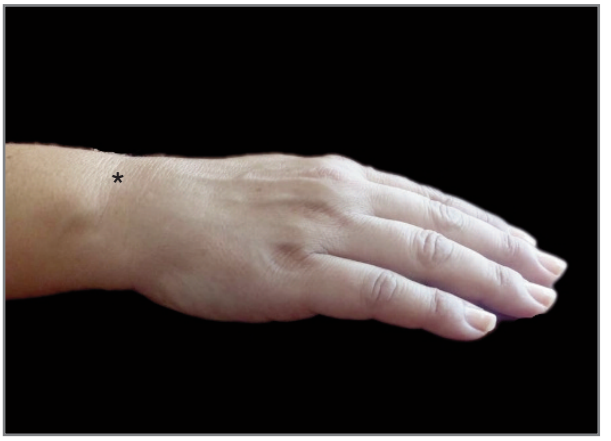

**FIGURE 1.** Swelling of the right wrist

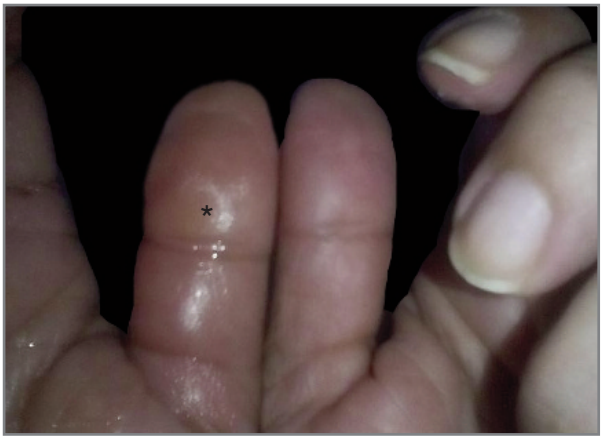

**FIGURE 2.** Dactylitis of the first finger of the right hand

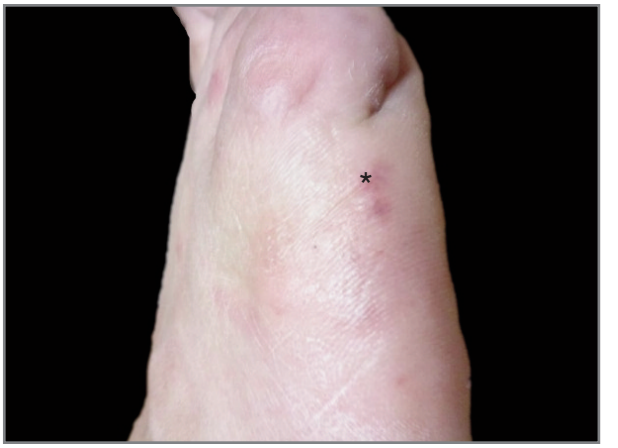

**FIGURE 3.** Painful lesions suggestive of Osler's nodules

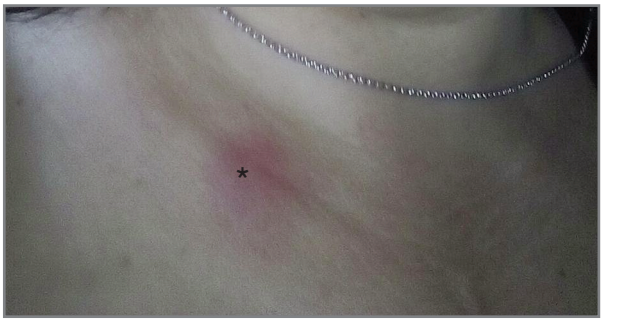

**FIGURE 4.** Small migratory and painful erythematous papules

tion detected caries in tooth 46, considered as the probable starting point of endocarditis, and extraction was performed.

During antibiotic therapy, the patient had full resolution of the musculoskeletal and cutaneous manifestations and the inflammatory parameters normalized.

## DISCUSSION

This case emphasises that IE may have a subacute presentation exclusively with unusual clinical manifestations such as arthritis, soft tissue swelling and migratory skin lesions; if unrecognised as IE symptoms and signs, the diagnosis may be delayed with impact on prognosis. In fact, given the wide range of clinical symptoms, IE is not always the most obvious diagnosis and other are considered firstly such as chronic infection, malignancy, rheumatological and neurological diseases. Therefore, as the patient might first present to a speciality other than Cardiology, it is important to always keep a high level of suspicion, mainly in at-risk patients[1].

Duke's criteria continue to be the most used in the diagnosis of infective endocarditis[3]. This patient met the Modified Duke Criteria for definite IE presenting 1 major criteria (identification of a microorganism from HACEK group on blood cultures) and 3 minor criteria (predisposition for IE conferred by the prosthetic valve, vascular phenomena manifested through spleen infarcts and immunological phenomena with the presence of Osler's nodes)[1].

The presence of musculoskeletal symptoms in patients with IE is not infrequent with prevalence ranging from 25% to 44% according to different studies and may be the presenting manifestations of the IE antedating the diagnosis by weeks to months[1, 2, 4-8]. However, they are often overlooked[4]. Several studies have tried to describe the frequency of different musculoskeletal symptoms among IE patients (Table I). The most frequently reported symptoms are arthralgia, peripheral arthritis, myalgia and back pain[1, 2, 6-9]. Peripheral arthri-

**TABLE I. THE PREVALENCE AND DESCRIPTION OF THE MOST COMMON MUSCULOSKELETAL MANIFESTATIONS PRESENT IN PATIENTS WITH INFECTIVE ENDOCARDITIS ACCORDING TO DIFFERENT STUDIES**

| Study | Meyers et al. South Africa (1977) | Churchill et al. Minnesota - USA (1977) | Thomas et al. France (1984) | Roberts-Thomson et al. Australia (1991) | González-Juanatey et al. Spain (2001) |
|---|---|---|---|---|---|
| Total of cases, n | 180 | 192 | 108 | 87 | 110 |
| Presence of musculoskeletal symptoms, n (%) | 50 (28%) | 84 (44%) | 32 (30%) | 22 (25%) | 46 (42%) |
| Arthralgia, n (%) | 19 (11%) | 32 (17%) | 17 (16%) | 2 (2%) | 17 (15%) |
| Arthritis, n (%) | 14 (7%) | 26 (14%) | 8 (7%) | 8 (9%) | 15 (14%) |
| Myalgia, n (%) | 19 (11%) | 27 (14%) | 5 (5%) | NA | 17 (16%) |
| Back pain, n (%) | 15 (8%) | 19 (10%) | 8 (7%) | 13 (15%) | 14 (13%) |
| Less frequent musculoskeletal manifestations, n (%) | Tenosynovitis, n= 2 (1%) | Nail Clubbing, n= 4 (2%); hypertrophic osteoarthropathy, n=1 (0.5%); Achilles tendinitis, n=1 (0.5%); avascular necrosis of the hip n=1 (0.5%). | Sacroiliitis, n=1 (0.9%); vertebral osteomyelitis, n=4 (4%) | NA | Sacroiliitis, n=1 (0.9%); leukocytoclastic vasculites, n=4 (4%) |

NA = not available

tis, usually affects only one joint although oligo- and polyarticular involvement have also been described, and it involves mainly large joints, predominantly of the lower limbs[2, 7-9]. The synovial fluid is sterile in the majority of cases, although one study showed positive synovial fluid cultures in half of the patients[2, 6, 9]. Migratory arthralgia as in our patient is uncommon[10]. Back pain is a frequently reported symptom particularly when associated to spondylodiscitis or vertebral osteomyelitis[6, 8, 10]. Less frequent, but also reported are sacroiliitis, polymyalgia rheumatic-like symptoms and cutaneous leucocytoclastic vasculitis[1, 2, 4, 11].

Infectious endocarditis can also give rise to clinical pictures mimicking rheumatic diseases[5]. Some clinical reports described patients with IE presenting with musculoskeletal manifestations and a positive RF, leading to the wrong diagnosis of rheumatoid arthritis. Actually, RF can be positive in about 36% of definitive cases of infectious endocarditis. A strong immune response generated by a chronic intravascular infection may be responsible for the development of the RF[3, 5]. Thomas *et al.* showed that the presence of RF contributes to a significantly delayed diagnosis compared to patients without rheumatoid factor[9]. IE may present with features suggesting polymyalgia rheumatica, such as neck, shoulder and pelvic girdles pain, with increased inflammatory parameters[11]. The presence of constitutional symptoms, fever, skin and visceral involvement may also resemble systemic vasculitis[12]. Another misleading factor is that ANCA may be positive in about 25% of patients[13]. Regarding skin manifestations, Osler's nodes, Janeway lesions and splinter hemorrhages typical of IE may mimic vasculitis and purpura should raise attention for embolic diseases[13, 14]. Visceral involvement, mostly renal, but also lung and cerebral, may point to medium vessel vasculitis. IE mimicking anti-neutrophil cytoplasmic antibody-associated small vessel vasculitis and pulmonary-renal syndrome was also reported in the literature[5].

Several studies tried to find epidemiologic, clinical and microbial differences between patients with IE with or without musculoskeletal symptoms. González-Juanatey study showed that patients with rheumatic manifestations most often came from rural regions and presented more commonly with microhematuria and with embolic complications, although no difference in mortality was found[2]. Thomas *et al*. revealed that microscopic haematuria and Streptococcus D infection were more frequent in patients presenting with musculoskeletal symptoms. Also, these patients had a diagnosis more frequently delayed and early death was more frequent[9].

Although pathogenesis of musculoskeletal symptoms is not well understood, several mechanisms have been postulated such as circulating immune complexes and deposition of bacterial emboli[7, 10]. Musculoskeletal symptoms seem to respond quickly once the endocarditis is treated[6-9].

Prosthetic valve IE occurs in about 1-6% of patients with valve prostheses and affects mechanical and bioprosthetic valves equally. Since clinical presentation is usually atypical and blood cultures and echocardiography are frequently negative, diagnosis of prosthetic valve IE is more difficult than the one of native valve IE[1].

According to 2015 European Society of Cardiology Guidelines for the management of infective endocarditis, transthoracic echocardiography is the first-line imaging exam in case of suspected IE, however in patients with prosthetic heart valves, a TOE is recommended although identification of vegetations might be particularly difficult with up to 30% of cases having a normal or inconclusive echocardiography, as in our case[1].

Overall, IE caused by a microorganism of HACEK (Haemophilus species, Aggregatibacter species, *Cardiobacterium hominis*, *Eikenella corrodens*, and Kingella species) group is rare and usually gives rise to atypical pictures of insidious evolution.[11, 15] This group consists of gram-negative organisms of slow growth[15]. Particularly, *Aggregatibacter actinomycetemcomitans* are usually oropharyngeal commensals, which gives strength to the theory that a periodontal infection was the source of the IE. In fact, they may gain access to the vascular compartment following oral hygiene procedures or mastication, dental infection, or less frequently during dental surgical procedures[15]. The standard treatment of IE caused by this type of microorganisms is monotherapy with intravenous ceftriaxone at 2 g daily at least during 6 weeks[1, 15].

Concluding, the diagnosis of IE is not always straightforward especially in subacute or chronic presentations with atypical symptoms. Musculoskeletal manifestations are relatively common but frequently underestimated. When suspected, particularly in patients with risk factors for IE, performing blood cultures and a transthoracic echocardiogram should be considered[5]. Considering that immunosuppressive therapy is the treatment for many rheumatologic diseases that IE may mimic and that it may aggravate the

underlying systemic infection it s important to keep this diagnosis in mind[1,5]. A multidisciplinary approach is also important since IE can affect different organ systems[1]. In this particular case, patient's collaboration should also be emphasized since objective examination was always very scarce and unspecific and the pictures shared by the patient helped reaching the diagnosis.

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