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CASE REPORT

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Staphylococcus aureus-induced septic arthritis of the ankle related to *malum perforans* in a diabetes patient

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Abstract

Septic arthritis (SA) is a less common joint pathology with potentially fatal outcome. It is considered a medical emergency, in which prompt diagnosis and differentiation of bacterial etiology is essential for appropriate management. The knee is the most prevalent site for SA (~50% of cases), followed by hip, shoulder, and elbow. Early intervention requires an accurate diagnosis and imaging techniques enable both a positive diagnosis, as well as arthrocentesis and liquid analysis, the "gold standard" criteria. We report the case of a 70-year-old patient, with history of rheumatoid arthritis (RA), diabetes mellitus (DM) and persistent left *malum perforans* in the last year, with development of a severe and debilitating *Staphylococcus aureus*-related SA of the left ankle, which posed significant therapeutic challenges. He developed a plantar lesion at the ball of the left foot, in the past one year, which was labeled as *malum perforans* in the setting of DM. Musculoskeletal ultrasound was the primary imaging technique used to define the location and extent of the infectious process. Cultures drawn from the tissue were positive for *S. aureus*. After an antibiotic course, the apparent infectious features were remitted but the long-lasting open wound failed to improve. Antibiotic therapy was initiated in accordance with culture sensibility tests but short- and long-term outcome was unfavorable with both treatment unresponsiveness and comorbidity burden posing considerable difficulties. The association and interrelation between different comorbidities (such as hypertension, diabetes, or obesity), chronic systemic inflammation (*e.g.*, C-reactive protein level, disease activity), and RA medication is sometimes difficult to understand and to address in daily practice, and this case report highlights multiple toils encountered in a SA patient with RA on immunosuppressive therapy and complicated DM.

Keywords: septic arthritis, imaging methods, rheumatoid arthritis, diabetes.

Introduction

Septic arthritis (SA) is a less common joint pathology with potentially fatal outcome. It is considered a medical emergency, in which prompt diagnosis and differentiation of bacterial etiology is essential for appropriate management. The knee is the most prevalent site for SA (~50% of cases), followed by hip, shoulder, and elbow [1]. SA develops either through hematogenous spread, direct inoculation, or extension from a contiguous infected tissue. Based on etiology, SA is generally divided in gonococcal and non-gonococcal arthritis. Of the latter, most cases involve a *Staphylococcus aureus* (*S. aureus*) or *Streptococcus* species (*Streptococcus* spp.) infection. Multiple factors related to both host immunity and bacterial pathogenesis influence the severity of the disease [2]. Typical risk factors for developing SA include age >80 years, diabetes mellitus (DM), rheumatoid arthritis (RA), joint surgery (<3 months ago), hip or knee prosthesis, skin or human immuno-deficiency virus (HIV) infection [1]. In contrast to gonococcal arthritis, non-gonococcal forms have a lower response rate to antibiotics and poorer prognosis. Overall, mortality rate in treated in-hospital SA patients can reach 15% [3].

Early intervention requires an accurate diagnosis and imaging techniques enable both a positive diagnosis, as well as arthrocentesis and liquid analysis, the "gold standard" criteria. Modern imaging methods, such as musculoskeletal ultrasonography, might add important advantages in both diagnosis and management of the rheumatic diseases. Musculoskeletal ultrasound (US) is a fast, reproducible, low-cost technique, which can be easily

used in any articular pathology for differential diagnosis and joint aspiration, in case of articular effusion [4–8]. Along with laboratory studies, enables an early diagnosis and proper therapeutic approach, as cartilage damage occurs very fast after the onset of infection.

Aim

We report the case of a 70-year-old patient, with history of RA, DM and persistent left *malum perforans* in the last year, with development of a severe and debilitating *S. aureus*-related SA of the left ankle, which posed significant therapeutic challenges.

Case presentation

A 70-year-old patient was admitted to the Department of Rheumatology, Emergency County Hospital, Craiova, Romania, in May 2018, following an ongoing and worsening pain and swelling of the left ankle in the last two months. The patient has a long history of type II DM, with secondary neurological and vascular complications. Other past disease history included a coronary angioplasty 14 years ago and arterial hypertension. Home medication consisted of antihypertensive drugs, oral antidiabetics, and platelet antiaggregant. He has had persistent arthralgias in the hands for the past four years which we're recently labeled as seropositive RA.

Since diagnosis of RA, the patient was started on Leflunomide and Sulfasalazine immunosuppressive drugs.

He developed a plantar lesion at the ball of the left foot, in the past one year, which was labeled as *malum perforans* in the setting of DM. The ulceration has since persisted and started to display features of an infectious process with purulent discharge after four months. At that time, the patient was managed in an Orthopedic Department for local debridement and close follow-up. Cultures drawn from the tissue were positive for *S. aureus*. After an antibiotic course, the apparent infectious features were remitted, but the long-lasting open wound failed to improve.

Upon admission in the Rheumatology Clinic, the patient presented with intense pain in the left ankle, with marked joint instability, limited range of motion and need of a walking aid and ankle orthosis. On physical examination, the ankle joint showed overall swelling, erythema, tenderness, and increased pain during movement. Local weightbearing could not be performed. Other joint symptoms were not evident, with no apparent signs of an active RA. Results of blood tests on admission showed an important inflammatory syndrome, with high values for both erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and a moderate anemia, with normal erythrocyte indices. The results are shown in Table 1. The patient underwent multiple US examinations for guided fluid aspiration and follow-up. An X-ray and magnetic resonance imaging (MRI) of the left ankle were also performed.

Imaging evaluation

Musculoskeletal US was the primary imaging technique used to define the location and extent of the infectious process. On admission, US assessment revealed significant changes related to a potential joint infection (Figures 1 and 2). Anterior scans displayed increased joint effusion of the tibiotalar joint, with extension on the lateral aspect of the joint. Marked tenosynovitis of the *peroneus longus* and *peroneus brevis* tendons was also detected. The joint effusion displayed an overall inhomogeneous hypo-echogenic content with scattered hyperechoic spots. Following close examination of the extent of the joint collection, an US-guided fluid aspiration was performed. A total of 30 mL of joint fluid was evacuated and microscopic analysis of the sample drawn displayed evident purulent features. The sample was sent for further cytology and microbiology studies. Confirmation of a *S. aureus* etiology through positive joint fluid culture allowed for a targeted antibiotic therapy course. During the follow-up period, the patient underwent additional US exams. Although no significant change was seen in the following scans regarding the quantity of joint effusion, further fluid aspiration failed to obtain significant samples due to a very thickened content. A slight benefit for better aspiration was obtained through joint lavage using saline solution. Left ankle MRI scans confirmed the presence of arthritis and tenosynovitis with additional diffuse bone edema of the tibial epiphysis, talus bone (Figures 3 and 4). X-ray image displayed important structural changes in the form of cortical irregularities, peri-articular demineralization, and joint space-narrowing.

Table 1 – ***Laboratory investigations***

Analysis	Result	Reference range
Hemoglobin	8.55 g/dL (*normal erythrocyte indices)	12.6–17.4 g/dL
Leukocyte count	7.418/mm^3	4000–10000/mm^3
CRP	152 mg/L	0–5 mg/L
ESR	86 mm/1 h	1–10 mm/1 h
Fasting glucose	122 mg/dL	70–110 mg/dL
Urea	37 mg/dL	18–55 mg/dL
Creatinine	0.84 mg/dL	0.72–1.25 mg/dL
AST	20 U/L	5–34 U/L
ALT	16 U/L	3–55 U/L
Joint fluid analysis		
Cytology	Numerous leukocytes, mononuclear cells, erythrocytes, and abundant detritus.	
Culture	Positive for *Staphylococcus aureus*.	

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CRP: C-reactive protein: ESR: Erythrocyte sedimentation rate.

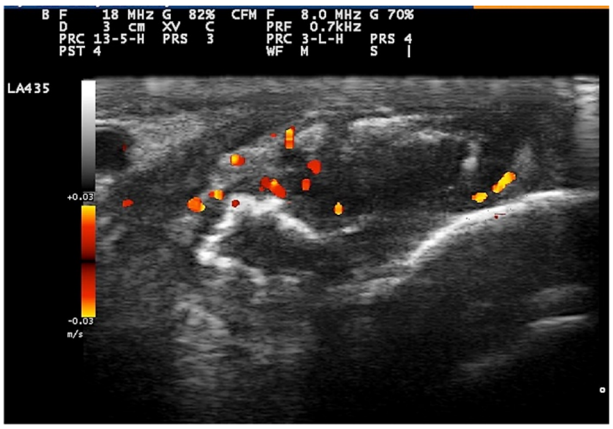

Figure 1 – ***Peroneus tendon sheath filled with heterogeneous material and marked irregularities of distal fibular bone cortical. Ultrasound image, short axis.***

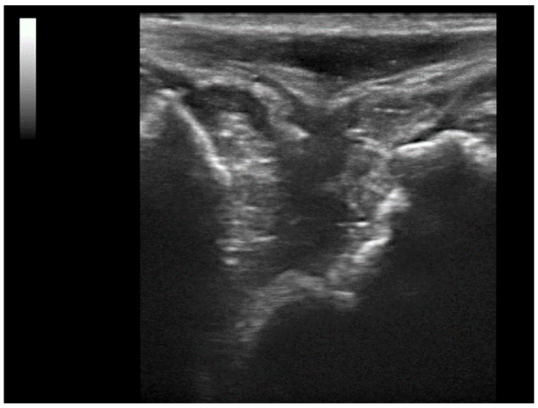

Figure 2 – ***Tibiotarsal synovitis with overall inhomogeneous joint collection, with hyperechoic floating conglomerates. Ultrasound image, long axis.***

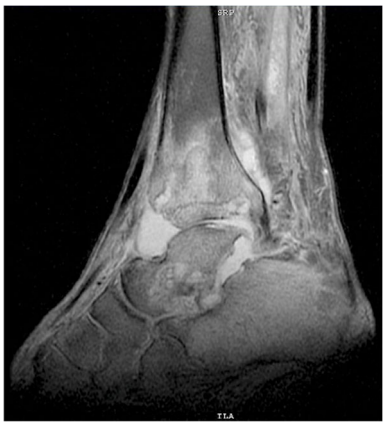

Figure 3 – ***Hyperintense signal suggesting marked bone marrow edema and intense tibiotarsal and subtalar joint synovitis. MRI of the ankle, sagittal FS PD-FSE. FS PD-FSE: Fat-suppressed proton-density fast-spin-echo; MRI: Magnetic resonance imaging.***

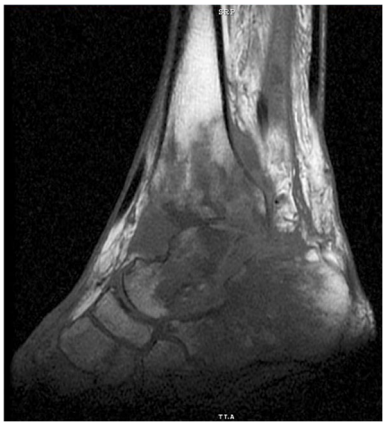

Figure 4 – ***Hypointense signal at the level of the tibia, talus, and calcaneus bone. Marked lysis of the aforementioned bones. MRI of the ankle, sagittal, T1 (longitudinal relaxation time) FSE image. FSE: Fast-spin-echo; MRI: Magnetic resonance imaging.***

Management and outcome

Antibiotic therapy was initiated in accordance with culture sensibility tests. We opted for a 14-day intravenous course of fluoroquinolone – Moxifloxacin 800 mg/day. Non-steroidal anti-inflammatory, analgesic and Sulfasalazine therapy was maintained, with discontinuation of Leflunomide. The patient displayed clinical improvement after one week, with pain reduction and better range of joint movement. Unfortunately, the apparent clinical response did not correlate with the follow-up US scans, which revealed persistent joint and peritendinous effusion.

The plantar lesion showed no development of local inflammation or infection, and surgical approach was not recommended at that point.

Before ending the two-week antibiotic course, the patient developed acute decompensated heart failure, massive pleural effusion and was referred to the Cardiology Department. The opportunity for surgery was once again postponed following this flare and fluoroquinolone therapy was extended for additional two weeks. The patient was lost to follow-up after discharge from Cardiology Department. Short- and long-term outcome was unfavorable with both treatment unresponsiveness and comorbidity burden posing considerable difficulties.

Discussions

Patients diagnosed with SA usually present a mono-articular pattern of joint involvement and associate one or more risk factors. SA with absence of risk factors is reported in 22% of cases [9]. An underlying joint pathology, such as RA, is the most common risk factor associated with SA. In general, up to 47% of SA patients have a history of joint pathology [10]. RA in particular poses multiple risks for bacterial infection, because of joint lesions, poor skin condition and immunosuppression. Studies on large case series of patients with SA, cite the presence of RA in 10–40% of SA cases [11]. In the presence of an existing RA or prosthetic joint, incidence of SA rises from 10 to 70 cases per 100 000 individuals [12]. Data from a population-based study by Doran *et al.* [13] indicate to a higher risk for severe infections requiring hospitalization in RA patients *versus* non-RA patients, with a rate ratio of 1.88. SA in particular was linked to the highest incidence risk in this study, with a rate ratio of 21.66 [1]. DM can also act as a double risk factor, through both compromised immunity and development of skin ulcers [9, 14, 15]. Our patient was considered a high-risk case, in which combined risk factors related to both RA and DM led to a high susceptibility for joint infection.

The diagnosis of SA in individuals with RA is usually delayed because of flare-like presentation of the infectious disease.

A poor prognosis observed in most of RA patients can be related to a difficult early diagnosis and to the immuno-compromised status, due to disease itself or immuno-suppressive treatment.

Although RA is a well-established risk factor for SA, the independent effect of specific disease-modifying anti-rheumatic drugs (DMARDs) is a debatable topic. Edwards *et al.*, in 2016, compared incidence rate ratios of SA for DMARD and non-DMARD RA patients [16]. The study reported significant differences only for Sulfasalazine (1.74) and Prednisolone (2.94), while other DMARDs, including Methotrexate and Leflunomide, did not show significant effects. Upon further analysis, the authors concluded that RA in itself should be considered a more relevant risk factor than any drug in particular and that

the apparent link to DMARD usage can be underlined by a high disease activity [16]. The most frequent infectious events related to DMARD use are the respiratory tract infections. Wolfe *et al*. (2006), reported specific RA treatment risks for lung infection and labeled Leflunomide as an independent risk factor for pneumonia [odds ratio (OR) 1.2] [17]. RA patients on combination DMARD therapy have an increased the incidence of fever/infection as opposed to individuals on monotherapy [18]. There is a general concern about the DMARD maintenance throughout an infectious episode. It is a common practice to discontinue DMARDs in the presence of a serious infectious event which requires hospitalization and intravenous antibiotics, with resumption of therapy after recovery [19].

Imaging studies are an integral part of the management of SA patients. MRI has a very high sensitivity, of nearly 100%, in diagnosing joint effusion, synovitis and bone or cartilage destruction [20]. Musculoskeletal US provides also a significant diagnostic performance with further advantages regarding availability, low cost and crucial aid in guided fluid aspiration or synovial biopsy [21]. Presence of joint fluid is the hallmark feature of SA on US. Depending on the time from onset, joint effusion may be hypoechoic or hyperechoic with blurred demarcation from synovial tissue [22]. Gaigneux *et al.* reported high prevalence of over 90% for both joint effusion and synovitis on US in a group of 34 patients with SA [20]. These changes persisted in a significant proportion of cases even after three months of therapy. Synovial hypervascularity was also common (64.3%) and could be associated with functional outcome. Residual lesions including synovial thickening, cellulitis and bone edema can be detected even after infection eradication [23].

The cornerstone of SA treatment is the adequate drainage through arthrocentesis or surgical approach coupled with parenteral antibiotics. If initial needle aspiration does not provide fast relief or the purulent fluid is too thick for aspiration, open drainage through arthroscopy or arthrotomy are strongly recommended. Some studies found superior results for surgical approach in deeper joint, such as the hip or shoulder [24–26]. Patients who are unfit for surgery can benefit also from joint washing by means of an irrigation–drainage system, especially in the knee joint [27]. In our approach, joint drainage was improved through saline solution irrigation and aspiration. Intra-articular corticosteroids are generally avoided in the setting of SA. Some authors address the benefit of this approach in patients which followed adequate systemic antibiotic and have persistent synovitis with sterile joint fluid and blood culture [28, 29].

A complex imagistic and laboratory assessment allowed us to establish an accurate diagnosis, but the several associated risk factors and consecutive complications did not allow us to apply all the necessary therapeutic measures, making the case difficult to have a good short- and long-term good prognosis [30, 31].

Conclusions

Early diagnosis and prompt antibiotic treatment are crucial for SA management. Outcome is generally worse in the presence of an underlying joint pathology. The association and interrelation between different comorbidities (such as hypertension, diabetes, or obesity), chronic systemic inflammation (*e.g.*, CRP level, disease activity), and RA medication, is sometimes difficult to understand and to address in daily practice and this case report highlights multiple toils encountered in a SA patient with RA on immunosuppressive therapy and complicated DM. Several factors contributed to the high risk of infectious disease, limitation of treatment and insufficient response.

Conflict of interests

The authors declare that they have no conflict of interests.

Authors' contribution

Andreea Lili Bărbulescu and Ştefan Cristian Dinescu have equally contributed to this paper.

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