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A CASE OF COMPLICATED PEDIATRIC SEPTIC ARTHRITIS OF THE KNEE CAUSED BY PANTON-VALENTINE LEUCOCIDIN-PRODUCING *STAPHYLOCOCCUS AUREUS*

S. SPOLAORE[1], R. BUGANZA[2], G. PRUCCOLI[3], I. TARDIVO[4], A. VERSACE[4], C. SCOLFARO[3], A. ANDREACCHIO[5]

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[1]Pediatric Orthopaedic Unit, Regina Margherita Children's Hospital, Turin, Italy
[2]Department of Public Health and Pediatric Sciences, Regina Margherita Children's Hospital, Turin, Italy
[3]Infectious Diseases Unit, Regina Margherita Children's Hospital, Turin, Italy
[4]Pediatric Emergency Unit, Regina Margherita Children's Hospital, Turin, Italy
[5]Pediatric Orthopaedic Unit, Vittore Buzzi Children's Hospital, Milan, Italy

Corresponding Author
Buganza Raffaele, MD; e-mail: buganzaraffaele@gmail.com

ABSTRACT – *Background:* Panton-Valentine leucocidin (PVL) is a toxin that may be expressed by *Staphylococcus aureus*, the pathogen most commonly responsible for musculoskeletal infections in children.

Case presentation: We presented a case of an 11-year-old boy with septic arthritis of the knee due to PVL-producing methicillin-resistant *Staphylococcus aureus* with complicated evolution. Repeated surgical procedures and prolonged antibiotic therapy were required for the resolution of the infection.

Conclusions: In children, musculoskeletal infections caused by PVL-producing strains of *Staphylococcus aureus* are characterized by increased morbidity and more frequent complications. Physicians' awareness of PVL, even in countries where PVL-positive SA is less common, is essential since early diagnosis and proper treatment can avoid serious local and systemic sequelae.

KEYWORDS: Panton-Valentine leucocidin, *Staphylococcus aureus*, Septic arthritis.

INTRODUCTION

Septic arthritis in children can lead to serious local and systemic consequences, as joint destruction, growth plate damage, angular deformity, septicemia. *Staphylococcus aureus* (SA) is the pathogen most commonly associated with musculoskeletal infections in children, and it may express toxins as Panton-Valentine leukocidin (PVL)[1], which is more common in methicillin-resistant SA (MRSA) than in methicillin-susceptible SA (MSSA)[2]. PVL is a synergohymenotropic toxin with two nonassociated components acting synergistically on membranes of polymorphonuclear leukocytes, monocytes and macrophages[3-5]. The two components, LukS-PV and LukF-PV are secreted before they assemble into a pore-forming heptamer, which bind to complement receptors on the target cells inducing membrane channel formation and cell lysis; the toxin also induces the release of pro-inflammatory cytokines and nuclear factor-kappa B in neutrophils[3-5]. The incidence of

PVL-positive SA varies widely by region. In United States and Colombia[2,6], 60-100% of Community-Associated MRSA (CA-MRSA) carry PVL genes and, in children with septic arthritis in Texas, 61% of SA were found[7] to be PVL-positive. Recent studies[8,9] documented the emergence and the increasing prevalence of PVL-positive CA-MRSA in Europe, where CA-MRSA infections occur far less commonly[2]. In 2016, in a multicenter European study[10] on pediatric CA-SA infections (7.8% MRSA, 92.2% MSSA), PVL was found in 18.6% of cases (22/118 strains) and, among the 70 SA in bone and joint infections, 17.1% of patients was PVL-producing. In the most recent multicenter European study[11] on pediatric osteoarticular infections, published in 2022 and reporting data from the EUCLIDS database, SA was identified in 57.1% (141/247) of microbiological confirmed cases, including 1 (0.7%) MRSA, but only 24 cases were investigated for PVL, which was detected in 25% (6/24) of the samples. In Italy, PVL is still an emerging problem, but it has not been adequately recognized as in other countries[12]. PVL-positive SA, known for causing skin and soft tissue infections (SSTIs), was also found in children with life-threatening infections, such as necrotizing pneumonia, necrotizing fasciitis and osteomyelitis[13].

CASE PRESENTATION

A 11-year-old boy was admitted at Emergency Department for left knee pain. Local trauma with superficial skin wound two weeks before and other two falls on the same knee in the previous days were reported. Knee X-ray was normal, and he was discharged. In the following days, he presented growing pain and fever and he was re-evaluated: blood tests showed mildly elevated C-reactive protein (CRP) and neutrophilic leukocytosis; arthrocentesis was performed but no fluid was obtained. Oral amoxicillin-clavulanate was started. Three days later, magnetic resonance (MR) evidenced significant intra-articular effusion (Figure 1) and he was admitted to our Emergency Department. A second arthrocentesis was performed, and synovial fluid resulted consistent with septic arthritis (cloudy aspects, red color, glucose 1 mg/dl, total proteins 5.8 g/dl, leukocytes 7,500 x10^9/l, 80% polymorphonucleocytes). Laboratory tests showed increased inflammatory markers (leukocytes 17.9 x10^9/l, CRP 161 mg/l, procalcitonin 3.17 ng/ml). Intravenous teicoplanin and amoxicillin-clavulanate were started. Two days later, fever and joint swelling increased, and surgical joint wash, curettage and placement of drainage were performed. Cultures of synovial fluid, from this sample and from the previous arthrocentesis, tested positive for MRSA and the two antibiograms showed resistance to penicillins, gentamycin, clindamycin, tetracycline and fusidic acid. Amoxicillin-clavulanate was replaced by rifampicin, maintaining teicoplanin. Two days later the drainage was removed. In the following days inflammatory markers decreased, but he presented remitting fever with high peaks. Teicoplanin was replaced by intravenous linezolid and then meropenem was started instead of rifampicin because a new antibiogram of pus sample from the wound showed resistance to this drug, in addition to those already identified in previous antibiograms. The fever persisted and eleven days after the admission a second MR (Figure 2) still showed joint effusion

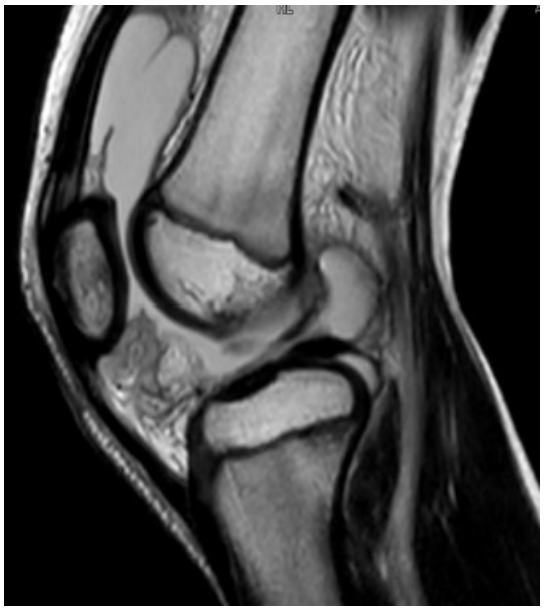

Figure 1. Magnetic resonance at diagnosis.

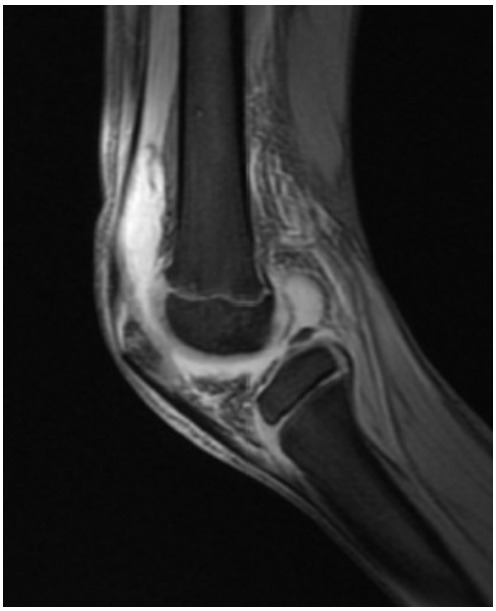

Figure 2. Magnetic resonance 1 week after the first surgical joint wash and curettage.

and synovial thickness. Considering the worsening clinical condition, five days later, knee arthroscopy with synovectomy (the synovial tissue was widely hypertrophic and inflammatory with some areas with bluish-red nodular appearance with vascular spots) and placement of drainage with continuous joint wash was performed. Synovial fluid culture still tested positive for MRSA resistant to clindamycin and rifampicin. Synovial fluid was tested for PVL and resulted positive. After the arthroscopy, clinical improvement, resolution of fever and normalization of inflammatory markers were noticed. Meropenem was discontinued, maintaining oral linezolid. Drainage was removed after twelve days. Three weeks later, MR evidenced significant improvement (Figure 3), with edema in periarticular space and soft tissue, but without intra-articular effusion, and the child was discharged. Linezolid was administered for overall 6 weeks; MR at 6 and 12 months (Figure 4) showed synovial thickness without growth plates damage and an asymptomatic osteochondral patellar lesion. The patient was asymptomatic and returned to swimming and snowboarding. Two years later he had mild lower limb length discrepancy (the left one was 1 cm longer), knee flexion had a 10° limitation, the extension was complete.

DISCUSSION

The role of PVL as a marker of severity is controversial: Shallcross et al[3], in a systematic review and meta-analysis, concluded that PVL-positive SSTIs were more often treated surgically, but there was no evidence that PVL affected outcome in pneumonia, bacteremia and colonizing strains. Current evidence[1,3,10,14] suggests that musculoskeletal infections in children caused by PVL-positive SA have increased morbidity, with more aggressive and rapid disease progression, more surgical interventions and complications (abscesses, pneumonia, deep vein thrombosis), longer duration of fever, longer intensive care unit admission, higher inflammatory markers[1].

In a recent systematic literature review, Bouiller and David[15] analyzed the studies between 2000 and 2022 reporting the genetic characteristics of SA and the outcomes of bone and joint infections: PVL genes resulted associated with poor outcomes in children, while no specific genes were similarly reported in adults[15].

In our case, the patient had high persistent fever, poor response to antibiotics and repeated surgical procedures. We excluded complications as local abscesses with MR, deep vein thrombosis with Doppler ultrasound and pulmonary, abdominal and cardiac involvement with chest X-ray, abdominal ultrasound and echocardiogram.

Where PVL-positive MRSA is common, toxin testing is not routinely performed; in some countries[3] it is recommended in CA invasive diseases or recurrent SSTIs SA infections. In pediatric osteoarticular infections, PVL should be suspected in particular if the patient or close family contacts have recurrent SSTIs infections or in cases of severe sepsis, multiple sites of infection/abscesses, extensive local lesions,

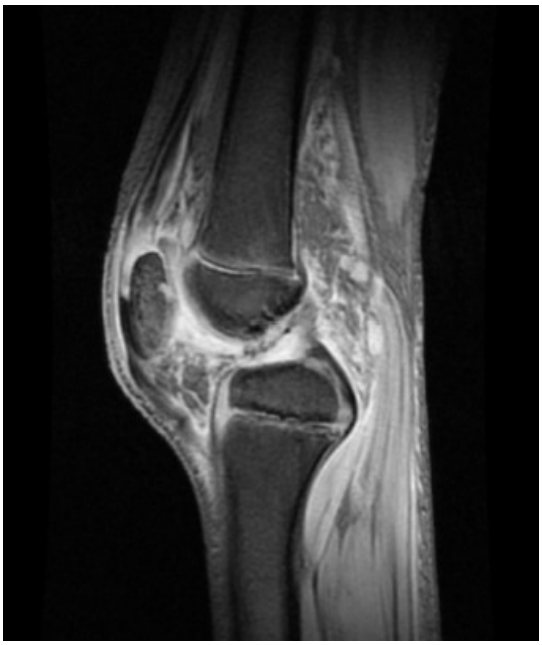

Figure 3. Magnetic resonance on discharge.

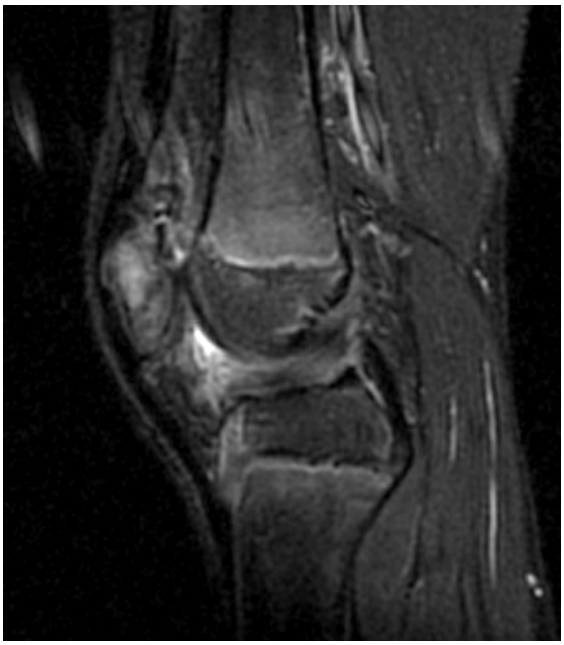

Figure 4. Magnetic resonance one year later.

myositis/pyomyositis, local venous thrombosis, very high CRP and repeated surgical procedures[16]. No other specific clue (not even with regard to the synovial liquid characteristics) to suspect its presence are reported in literature, but the knowledge of conditions related to PVL can lead to precocious diagnosis and adequate treatment, which are essential to avoid severe clinical consequences.

In osteoarticular infections with PVL-positive SA, aggressive early orthopedic intervention to drain focus of infection is recommended[16]. In septic arthritis of the knee in children, arthroscopic drainage plus antibiotic treatment is an effective treatment, also for recurrences[17].

PVL detection is important to guide antibiotic treatment. In cases of PVL-positive SA, sub-inhibitory concentrations of beta-lactams can enhance expression of PVL, while clindamycin, linezolid, fusidic acid and rifampicin are inhibitory and vancomycin, tetracycline, ofloxacin and co-trimoxazole have no significant effect[18]. According to the UK Health Protection Agency Guidance[16], in children, once PVL-positive SA is confirmed in deep-seated infections, intravenous clindamycin plus rifampicin, possibly with the addition of linezolid, is indicated. The linezolid alone for bone and joint infections could be effective, but it is limited by potential toxicity in prolonged therapy[4]. As continuation therapy for pediatric joint infections, clindamycin plus rifampicin is suggested[16].

In our case, considering the resistance to clindamycin and the subsequent resistance also to rifampicin (likely due to selection of resistant strains during antibiotic treatment), linezolid was administered for 6 weeks.

CONCLUSIONS

We reported a case of pediatric septic arthritis of the knee complicated by the high virulence of PVL-producing MRSA, which is related to difficult course of musculoskeletal infections with poor response to antibiotics and necessity of aggressive and sometimes repeated surgical procedures. Early detection of the toxin is crucial to define an appropriate treatment program to improve the outcome and PVL testing must be considered in the diagnostic path.

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SS, AA, RB and GP conceived the paper. SS, RB and GP wrote the manuscript and carried out the references search. SS, IT, AV, CS and AA have followed the patient over the time and reviewed the manuscript. All authors read and approved the final manuscript.

ORCID ID:
Spolaore S: 0000-0001-5241-7201; Buganza R: 0000-0003-1850-2300; Pruccoli G: 0000-0003-2250-6048; Tardivo I: n.a.; Versace A: n.a.; Scolfaro C: 0000-0001-9158-319X; Andreacchio A: 0000-0001-7729-3890.

Conflict of Interest:
The authors declare that they have no conflict of interest to disclose.

Availability of Data and Materials:
Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Informed Consent:
Written informed consent was obtained from the patient's parents for the publication of this case report.

Ethics Approval:
Not applicable.

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