Deep venous thrombosis associated with acute hematogenous osteomyelitis in children


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Summary
Introduction: Deep venous thrombosis (DVT) is rare in children. It may complicate acute hematogenous osteomyelitis (AHO).

Objective: The present study assessed the incidence of DVT in community-acquired AHO, and compared clinical and laboratory characteristics with AHO without DVT.


Results: Seventy patients were included: mean age, 7.7 years. Seven developed DVT. All involved Staphylococcus aureus. The isolated Staphylococcus aureus was significantly more often methicillin-resistant than methicillin-susceptible (p = 0.04). C-reactive protein, erythrocyte sedimentation rate, positive blood culture and incidence of pulmonary staphylococcus were significantly higher in patients with DVT. These patients also had significantly more febrile days. One patient with DVT died from severe refractory respiratory failure.

Discussion: DVT was observed in 10% of cases of community-acquired AHO. DVT was associated with more severe onset, with extensive local disease. Surgery was often needed to drain a subperiosteal abscess. DVT can cause invasive and life-threatening infection through septic emboli, particularly to the lungs.

Level of evidence: Level III.

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Introduction

Venous thrombosis is rare in children as compared to adults, but has become more common in recent years with the increase in severe forms of osteoarticular infection, notably implicating community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) [1].

We here report seven cases of acute hematogenous osteomyelitis (AHO) complicated by deep venous thrombosis (DVT), over a period of 32 months.

The objective was to determine the frequency and specificities of community-acquired AHO complicated by DVT in patients admitted to the Pediatric Orthopedics Department of the Tunis Children’s Hospital.

Patients and methods

A prospective study was run from the beginning of April 2007 to the end of December 2009 in the Pediatric Orthopedics Department of the Tunis Children’s Hospital. Cases of neonatal or nosocomial AHO and those secondary to direct inoculation or infection by contiguity were excluded. Diagnosis was based on clinical and biological signs of bone infection associated with positive bacteriological culture and/or subperiosteal collection on ultrasound (US) or, in case of negative culture without subperiosteal collection, on clinical and biological signs associated with magnetic resonance imaging (MRI) signs of bone infection and/or triple-phase metastable technetium 99 (99mTc)-labelled methylene diphosphonate bone-scan.

Patients systematically underwent inflammation assessment comprising blood count exploring hyperleukocytosis, C-reactive protein (CRP) assay and erythrocyte sedimentation rate (ESR) measurement. Standard infection-site and thoracic X-ray and US scan exploring for subperiosteal collection were also systematically performed on admission. Doppler sonography exploring for DVT was performed in case of local clinical signs.

Bacteriology comprised blood culture ahead of antibiotic therapy, with infection-site sampling in case of surgery.

Time of evolution before treatment, degree of fever and of functional impairment, CRP and ESR values at admission and leukocyte count per mm$^3$ were systematically recorded, as were the number of surgical operations required and the presence of remote, notably pleuropulmonary, locations.

Statistics

Data were analyzed on SPSS version 11.0 software. Means were compared by Student t-test and percentages by Pearson’s Chi$^2$. The significance threshold was set at $p \leq 0.05$.

Results

During the study period, 70 patients were admitted for AHO as diagnosed on the above criteria. Mean age was 7.7 years (range, 7 months—13.5 years). In 88% of cases, infection involved pelvic and lower-limb bones. Bacteriology was positive in 64.5% of cases, isolating *Staphylococcus aureus* (SA) in 86% of cases, including 33 cases of methicillin-susceptible *Staphylococcus aureus* (MSSA) and six of MRSA; other bacteria comprised *Streptococcus aureus* in 11% of cases ($n=5$), and salmonella in one patient with sickle-cell anemia.

Seven patients had DVT (10%), located in the lower limbs and pelvis in all cases. Table 1 shows DVT and associated AHO locations.

The mean age of DVT patients was 8.1 years (range, 23 months—13.5 years). Mean time to consultation was 4.4 days (0–7 days). All patients had significant bone pain causing total functional impotence. Fever was greater than 38 °C in all cases (mean = 38.6 °C). Five patients showed deteriorated general health status on admission and three had or went on to develop diffuse alveolar lesions in both pulmonary fields, with thoracic X-ray signs of pleuropulmonary SA infection.

CRP levels exceeded 72 mg/L, at a mean 251 mg/L on admission. ESR was consistently greater than 40 in the first hour, at a mean 84. Polynuclear neutrophil hyperleukocytosis was consistently greater or equal to 10,900/mm$^3$, at a mean 13,550 leukocytes/mm$^3$.

SA was isolated in all cases: four MSSA and three MRSA. Six patients showed positive blood culture. Bacteria were detected at the infection site in six patients. Six patients showed subperiosteal collection or deep infection-site collection and required surgery; four underwent iterative surgery to drain secondary collection.

One 13.5-year-old patient, admitted for AHO of the femur evolving for just a few hours, died; superficial femoral vein thrombosis had been diagnosed on arrival and was associated with subperiosteal collection. MRSA infection was suspected in light of the thrombosis and severe clinical aspect, and effective-dose teicoplanin was initiated on admission. Heparin therapy was initiated immediately and surgery was performed for subperiosteal abscess drainage. MRSA was isolated some days later and teicoplanin susceptibility was checked. During the following days, two other osteoarticular locations developed, requiring surgical drainage. Fever persisted, with respiratory distress and alveolar lesions in both pulmonary fields. The child was transferred to intensive care but died of respiratory distress 6 days after admission.

Table 2 shows the various clinical and biological data for the cases of AHO complicated by DVT, in comparison to DVT-free forms. Comparative analysis found significant differences in CRP and ESR values; blood culture was also significantly more often positive in case of DVT, as was time to apyrexia.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Locations of venous thrombosis and corresponding osteomyelitis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombosis</strong></td>
<td><strong>Osteomyelitis</strong></td>
</tr>
<tr>
<td>Sural</td>
<td>Tibia</td>
</tr>
<tr>
<td>Internal saphenous and superficial femoral</td>
<td>Proximal tibia</td>
</tr>
<tr>
<td>Popliteal and sural</td>
<td>Distal femur</td>
</tr>
<tr>
<td>Superficial femoral</td>
<td>Femur</td>
</tr>
<tr>
<td>Popliteal and sural</td>
<td>Proximal tibia</td>
</tr>
<tr>
<td>Popliteal and superficial femoral</td>
<td>Tibia</td>
</tr>
<tr>
<td>Left external iliac</td>
<td>Femoral neck</td>
</tr>
</tbody>
</table>
Discussion

Venous thrombosis is rare in children compared to adults, with annual incidence estimated at 0.06 to 0.07/10,000 versus 2 to 7/10,000 [2]. There are two childhood frequency peaks: neonates and under 1-year-old, and preadolescents and adolescents [3]; incidence is much lower in 2- to 14-year-olds. Risk factors are usually implicated, such as central venous catheterization (especially in infants), congenital prothrombotic factors, trauma, immobilization, surgery or, in adolescent girls, pregnancy [3].

DVT in association with AHO is being reported more and more frequently. Hollmig et al. [4] found 11 cases of DVT in 212 of AHO, and performed the only comparative study of AHO with and without DVT to our knowledge. Gonzalez et al. [5] reported nine cases of DVT associated with AHO. More recently, Vander Have et al. [1] reported eight cases of DVT complicating osteoarticular MRSA infection, usually AHO. These were the longest series we retrieved; smaller ones have also been published [6–9].

It is important to highlight the increase in frequency of such DVT over the last 10 or so years. This was particularly clear in Gonzalez’s series [5], where eight of the nine cases were diagnosed between 2001 and 2004 and only one during the 3 previous years.

In the present series, DVT was consistently located in the pelvis and lower limbs, and most often adjacent and/or proximal to the bone infection site. More superior (vena cava) locations have also been reported [4].

AHO complicated by DVT shows clinical, biological and evolutive specificities.

Mean age did not greatly differ with or without DVT in the present series. Hollmig et al. reported a mean age of 10.9 years in case of associated DVT, significantly older than in the other cases of AHO. In Gonzalez et al.’s series [5], the mean age was 10.6 years.

In the present series, the sex ratio in case of associated DVT was tilted towards boys (6:1), but did not significantly differ from that in the other cases of AHO. Such masculine predominance was also reported elsewhere: all the patients in Gonzalez et al.’s series were boys, as were eight of the 11 patients in Hollmig et al.’s [4] and all three patients in Gorenstein et al.’s [10]. Walsh and Phillips [8], in contrast, reported no such masculine predominance, three of their four patients being girls.

AHO complicated by DVT shows particularly intense clinical symptomatology, with rapid onset of severe pain and total functional impotence, observed as of admission in all the present series. Local signs are likewise severe, with edema often extending well beyond the implicated bone segment. In the present series, there were no significant differences in degree of fever at admission: 38.6 vs. 38.9 °C in AHO without DVT. Hollmig et al. [4], on the other hand, reported higher fever in case of DVT. The severity of the initial clinical aspect probably accounts for the shorter time to consultation in their series: 5.6 days in AHO with DVT vs. 14.4 days without; the present series showed no such significant difference. There was, on the other hand, a significant difference in the severity of the biological inflammatory syndrome at admission, especially in terms of CRP and ESR; no such difference was found for hyperleukocytosis. Bacteria were isolated in all patients with DVT, compared to 64.5% of the rest of the present series. Blood culture was likewise more often positive, at 86 vs 41%, indicating more severe septicemia in case of DVT. Surgery was also more often required in case of DVT, and mean time to apyrexia was significantly longer.

Occurrence of DVT was significantly associated with septic pulmonary locations. Three patients developed respiratory distress associated with pulmonary lesions suggestive of pleuropulmonary Staphylococcus infection. The radiological aspect of diffuse alveolar opacity in both pulmonary

### Table 2 Comparison of AHO with and without.

<table>
<thead>
<tr>
<th></th>
<th>With DVT n: 7</th>
<th>Without DVT n: 63</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>8.1</td>
<td>7.6</td>
<td>NS</td>
</tr>
<tr>
<td>Sex ratio</td>
<td>6</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Evolution (days)</td>
<td>4.4</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>38.6</td>
<td>39</td>
<td>NS</td>
</tr>
<tr>
<td>Leukocytes/mm³</td>
<td>13550</td>
<td>12911</td>
<td>NS</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>251</td>
<td>109</td>
<td>0.001</td>
</tr>
<tr>
<td>ESR (1st hour)</td>
<td>84</td>
<td>48</td>
<td>0.003</td>
</tr>
<tr>
<td>MSSA n (%)</td>
<td>4 (57%)</td>
<td>29</td>
<td>NS</td>
</tr>
<tr>
<td>MRSA n (%)</td>
<td>3 (43%)</td>
<td>3</td>
<td>0.04</td>
</tr>
<tr>
<td>SA n (%)</td>
<td>—</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
<td>Non-isolated n (%)</td>
<td>—</td>
<td>25</td>
<td>0.04</td>
</tr>
<tr>
<td>+ve blood culture (%)</td>
<td>6 (86%)</td>
<td>23 (36.5%)</td>
<td>0.02</td>
</tr>
<tr>
<td>+ve local sample n (%)</td>
<td>6 (86%)</td>
<td>28 (79%)</td>
<td>0.052</td>
</tr>
<tr>
<td>Operated n (%)</td>
<td>6 (86%)</td>
<td>34 (53%)</td>
<td>NS</td>
</tr>
<tr>
<td>Time to apyrexia (days)</td>
<td>12</td>
<td>3</td>
<td>&lt; 10⁻³</td>
</tr>
<tr>
<td>Pulmonary Staph. infection n (%)</td>
<td>3 (43%)</td>
<td>1 (1.4%)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MSSA: methicillin-susceptible Staphylococcus aureus; MRSA: methicillin-resistant Staphylococcus aureus; SA: Staphylococcus aureus; n: number of patients.

NS: non-significant.
Venous thrombosis and acute osteomyelitis

A central role of DVT in the spread of infection and particularly of pleuropulmonary infection by septic embolus release was suggested by Gorenstein et al. [10], three of whose patients showed signs of pulmonary involvement on standard X-ray. All patients showing DVT in Vander Have et al.’s series [1] developed respiratory distress requiring assisted ventilation. Seven of the 11 patients in Hollmig et al.’s series [4] showed pulmonary lesions suggestive of septic emboli, as did four of the nine patients in Gonzalez et al.’s series [5]. Many other publications have likewise reported AHO complicated by DVT to be associated with signs of septic pulmonary emboli [8,9,12].

Pulmonary involvement may in some cases be the only sign of DVT [9]. Local signs may be negligible, difficult to spot and masked by signs of AHO. In such cases exploration for DVT is mandatory. Diagnosis is based on venous Doppler sonography with good sensitivity and specificity; in case of doubt, angioscan or angio-MRI may also be used [2]. Involvement of a pulmonary location is a severe, potentially life-threatening complication. Such was indeed the case for one of our patients, despite early diagnosis leading to adapted antibioticotherapy, emergency surgical drainage and early heparin therapy. Gorenstein et al. [10] stressed the severe, life-threatening prognosis in case of associated AHO, DVT and septic pulmonary embolism.

DVT is a complication of SA infection. SA was found in all the patients of the present series: MRSA in three cases and MSSA in four. The former more frequently induced DVT than the latter: 50 vs 12%, which was a significant difference. Elevated frequency of DVT in case of MRSA was also reported elsewhere [1,4,5,13]. The increased incidence of AHO complicated by DVT in recent years matches the shift in AHO etiology [13–15], with an increase in MRSA infection.

The physiopathology of DVT in AHO seems to be unrelated to any congenital prothrombotic risk factor. Gonzalez et al. [5] explored hemostasis in eight of their nine patients, and found no congenital hypercoagulability that could account for the development of DVT. Hollmig et al. [4], on the other hand, found congenital prothrombotic risk factors in two of the nine patients explored. DVT is probably secondary to bacterial virulence factors, SA releasing bacterial enzymes, which interact with fibrinogenesis, inducing a clot. Bacterial exotoxins may induce platelet aggregation and vessel-wall smooth-muscle spasm, facilitating thrombosis [10]. Panton Valentine leukocidin (PVL) is one such toxin frequently found in case of DVT [5]: it is highly necrosing, inducing a severe acute clinical and biological profile, and may be produced by both MRSA and MSSA [16].

In conclusion, the risk of DVT is always to be borne in mind in case of AHO, especially when the aspect is severe, with very strong local and significant general signs. In presence of pulmonary lesions suggestive of septic emboli, exploration for DVT is also mandatory. If it is discovered, treatment should be energetic and surveillance tight; low molecular-weight heparin relayed by oral antivitamin K should be administered to prevent local extension of thrombosis and embolism. Use of intravascular filters has also been reported [5].

Adapted antibioticotherapy should target MRSA and PVL-secretating SA [16].

Conflict of interest statement
None.

References