Spinal epidural abscess complicating chemotherapy in patients with leukemia

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The authors reviewed the basic facts about infections that complicate chemotherapy, and found that a difference exists between those that are medically treated, for which several standard protocols have been adopted, and infections amenable to surgical treatment, such as spinal epidural abscess, which are managed according to the experience at individual institutions. The authors believe that patients with leukemia who manifest a spinal epidural abscess should always be surgically treated when the infection occurs between the induction and remission phases, whereas medical treatment options can be considered for spinal epidural abscesses occurring at the end of the chemotherapy course.

KEY WORDS • spinal epidural abscess • infection • chemotherapy • leukemia

Spinal epidural abscess is a rare⁹ and potentially life-threatening condition, with a very high morbidity rate and an overall mortality rate of 10 to 20%.^{2,3,29} In the largest series, investigators have stressed the importance of early diagnosis in providing adequate treatment,^{15,19} be it surgical decompression or conservative management.

Generally accepted risk factors for spinal epidural abscess are conditions of systemic immunocompromise such as human immunodeficiency virus, diabetes mellitus, alcoholism, and long-term corticosteroid treatment.^{7,22,25} Patients undergoing cancer treatment have also been recognized as an at-risk group^{25,29} for this pathological entity. Leukemia is not a rare condition; its incidence is 9.6 per 100,000 population per year (including both acute and chronic forms), and we believe that identification of basic guidelines for surgical treatment of infections in patients with leukemia would result in a better and safer treatment.

Infections in Patients With Leukemia

Infections related to immune system impairment occur in 60 to 100% of patients receiving high-dose chemotherapy and are the most frequent complication of treatment in patients with leukemia; they remain the principal cause of morbidity and mortality in 75% of these patients. During chemotherapy, the bone marrow of patients with leukemia undergoes profound and often prolonged periods of drug-induced myelosuppression (neutropenia for > 4 weeks). Antineoplastic agents, radiation therapy, and corticosteroid drugs all play a role²³ in promoting this condition, the first disrupting chemotaxis and phagocytosis and compromising the neutrophils' ability to eliminate intracellular microorganisms, whereas the other two contribute to delays in recovery of peripheral blood neutrophil counts.

Medical Treatment of Infectious Complications

A sudden drop in the peripheral neutrophil count (< 150 cells/ μ l) leaves patients vulnerable to life-threatening bacterial, viral, and fungal infections,^{8,23,24} and the outcome depends on early initiation of appropriate therapy. Unfortunately, prompt diagnosis of infection is difficult because early signs and symptoms may be absent or nonspecific, and laboratory and neuroimaging findings frequently are unremarkable. To complicate the issue, immunosuppressed patients may have multiple infections during a single clinical presentation. Therapy is often instituted empirically, based on the clinical presentation and symptoms. Initial therapy in patients with neutropenia who present with fever should cover the most common and life-threatening pathogens (Table 1).

The spectrum of the empirical antimicrobial treatment has to include Gram-negative aerobic bacteria^{4,7} (*Enterobacteriaceae* and *Pseudomonas aeruginosa*) and Gram-positive cocci (streptococci, enterococci, and *Staphylococcus aureus*), and should be adapted to local resistance. Initial therapy does not necessarily have to cover coagulase-negative staphylococci, oxacillin-resistant *S. aureus*, anaerobic bacteria, and fungi. In case of treatment failure (persistent fever or clinical instability), second-line therapy should include a glycopeptide, teicoplanin, or vancomycin, and should close antimicrobial activity gaps in the Gram-negative spectrum. If patients are clinically stable, a switch to second-line therapy should not be made earlier than 96 hours after the start of treatment, because some patients are slow to respond. Patients with an expected duration of neutropenia of more than 7 days and in whom clinical deterioration is observed should also be given parenteral antifungal therapy with amphotericin B or fluconazole.

Most infectious complications of medical interest in

Abbreviation used in this paper: MR = magnetic resonance.

TABLE 1
Pathogens and clinical syndromes in patients
with spinal infections

Microorganism	Clinical Syndrome
bacteria	
<i>Staphylococcus aureus</i> , coagulase-negative <i>S. spp.</i> , <i>Streptococcus haemolyticus</i>	bloodstream infections
Gram-negative <i>Escherichia coli</i> , <i>Klebsiella spp.</i> , <i>Ps. aeruginosa</i> , <i>Bacteroides spp</i>	bloodstream infections (infected central venous catheter or endovascular devices), pneumonia; gastrointestinal tract infections: necrotizing enterocolitis, peritonitis
<i>Clostridium spp</i>	subcutaneous infections: fasciitis, myositis
yeast	
<i>Candida albicans</i>	bloodstream infections, hepatosplenic abscesses
<i>Trichosporon beigeli</i>	hepatosplenic abscesses
fungi	
<i>A. fumigatus</i>	invasive pulmonary aspergillosis; other sites: brain, heart, liver, kidney
viruses	
herpes simplex virus type 1	mucositis, stomatitis, hemorrhagic
herpes simplex virus type 2	cystitis, interstitial pneumonia
varicella-zoster virus	
human cytomegalovirus	

patients with leukemia who are undergoing chemotherapy can be effectively managed. Both prophylaxis, accomplished by following the rules of hygiene and by administering routinely used antibiotics, and early recognition of the disease are essential for effective treatment.

Surgical Management of Infectious Complications

Management of infections requiring surgical treatment in patients with leukemia is not as codified as is medical therapy. In the literature, cases of infections of anorectal regions, small bowel obstruction after chemotherapy, life-threatening toxic megacolon, perforation of the bowel, and necrotizing enterocolitis have been reported.^{6,10,16,17,28} Antineoplastic agents such as etoposide or cytosine arabinoside, which are associated with severe gastrointestinal mucosal excoriation, increase the risk of some of these complications. The new purine analogs^{1,21,26} have been associated with opportunistic infections caused by uncommon microorganisms such as *Pneumocystis carinii*, *Listeria monocytogenes*, and fungi. Clinical parameters often are subtle, but high-grade unresponsive fever, abdominal pain, and diarrhea must be evaluated promptly.

In the literature we could not identify guidelines for surgical treatment of infections in patients with leukemia: the cases reported all highlight the lack of a standard protocol and the importance of the experience at a particular institution in handling such situations. Some agree on the desirability, when possible, of delaying surgery²³ until neutrophil counts improve, because recovery of functional neutrophil levels has a favorable impact on outcome. This requires a close monitoring of the complete blood count and infectious markers, which is not straightforward in

patients with leukemia, whose blood parameters are all out of the normal ranges.

Antineoplastic drugs have a very strong impact on the human immune system, and all cause different levels of myelosuppression, depending on their mechanism of action and target. Standard induction therapy in leukemia typically involves either a four-drug regimen of vincristine, prednisone, anthracycline, and cyclophosphamide or L-asparaginase, or a five-drug regimen of vincristine, prednisone, anthracycline, cyclophosphamide, and L-asparaginase given over the course of 4 to 6 weeks. Consolidation therapy includes cytosine arabinoside in combination with anthracycline or epipodophyllotoxin.^{13,14} Chemotherapeutic treatment of leukemia, compared with other malignancies such as breast or lung cancer,^{5,18} might be continued for a longer period of time, up to 2 years, and we believe that this peculiarly massive and prolonged immunosuppression renders patients with leukemia more exposed to dangerous infectious complications.

Spinal Epidural Abscess in Patients With Leukemia

Spinal epidural abscess complicating the chemotherapeutic course is a rarely described occurrence. In a review of the literature we identified a few cases of spinal infectious complications in patients receiving antileukemia treatment. Cases of spinal infections caused by opportunistic agents such as *Pn. carinii*, *L. monocytogenes*, and fungi are rare, as is vertebral osteomyelitis caused by *Aspergillus fumigatus*: only 39 cases have been described between 1966 and 1998, most of them occurring in patients with immune impairment.²⁷

Clinical presentation of spinal epidural abscess in immunocompromised patients might not include the classic triad of fever, high white blood cell count, and high erythrocyte sedimentation rate in laboratory tests as well as signs of radiculopathy or myelopathy. Initial signs and symptoms can be subtle, consisting of localized spinal pain, and later signs of myeloradicular compression might occur: these include radicular pain, paresthesias, muscle weakness, sensory loss, sphincter dysfunction, and finally paralysis.

Magnetic resonance imaging is the method of choice for diagnosis of spinal epidural abscess; Gd-enhanced MR images can aid in the categorization of the age and consistency of the lesion (that is, pus or granulation tissue), and this modality is helpful in defining the relationship of the abscess to nerve structures, revealing evidence of spinal cord compression, although no relationship between signs of compression on MR images and the rate of disease progression has been proved. Notably, MR imaging findings are helpful in planning appropriate interventions:²⁰ a solid appearance of granulation tissue requires a more extended laminectomy, whereas imaging findings of areas of liquid pus indicate the feasibility of limited laminotomies and washout of the epidural space to treat the abscess.

Spinal epidural abscess can be treated either surgically or conservatively. Indications for surgical treatment¹² include progressive neurological deficit, persistent severe pain, or persistent fever and leukocytosis despite adequate antibiotic therapy. We believe that in patients with leu-

Fig. 1. Contrast-enhanced T₁-weighted axial MR images. a: Preoperative MR image demonstrating signs of discitis at the L4–5 space and a related spinal epidural abscess, displacing the dural sac caudally and to the right side (*arrows*). b: Postoperative MR image demonstrating a peripheral rim of contrast enhancement. Imaging findings are nonspecific and cannot be used to discriminate between postoperative scarring and residual signs of epidural infection (*arrows*).

kemia the main concern is the timing of treatment: when rather than how to treat the abscess. In fact, the bone marrow of a patient with leukemia typically requires 2 to 3 weeks to recover after standard induction therapy, and postremission therapy is immediately initiated to prevent recurrence of leukemia and development of drug resistance.

We believe that a spinal epidural abscess occurring between the first and second phase of chemotherapy leaves no time to evaluate the effectiveness of antibiotic therapy, because failure of conservative management would result in a deferred intervention and in a delayed start of the second-phase consolidation chemotherapy, favoring relapse of leukemia. In our opinion a spinal epidural abscess developing after induction of chemotherapy should be surgically drained in any case: the choice of an adequate surgical approach is then mandatory to compromise between successful drainage of the abscess and minimally invasive surgery, especially for multilevel, extended abscesses. We believe granulation tissue that is tightly adherent to the dura mater should not be removed if this involves a risk of fissure in the dura mater itself, because spread of infection could occur through the cerebrospinal fluid.

We think that selection of appropriate treatment of spinal epidural abscess in patients with leukemia must be adjusted in relation to their chemotherapy schedule and to the presence of motor deficit. After surgery, consolidation chemotherapy should be initiated only when the infection has completely resolved. This might be difficult to prove because infection markers are quite out of range in these cases, and only a limited period of observation is possible before continuing chemotherapy. Careful monitoring of the patient's clinical condition and results of laboratory tests is mandatory.

Follow-up MR images can be useful in determining residual signs of infection, but postoperative findings are quite nonspecific, because a contrast-enhanced area might represent either postoperative scarring or a residual pus collection (Figs. 1 and 2). A bone scan performed with

gallium contrast at 6 weeks, if negative, might indicate that infection had resolved.¹¹ We believe that results of clinical examination together with laboratory tests and imaging findings should be considered in the postoperative follow-up review. Motor deficits improve slowly after surgical decompression, but lessening of preoperative pain could indicate resolution of epidural infection. When spinal epidural abscess occurs after the last chemotherapy treatment, the standard protocol currently adopted in the literature can be considered.

CONCLUSIONS

Standard guidelines for surgical management of these infections have not yet been identified, but there is a gen-

Fig. 2. Contrast-enhanced T₁-weighted sagittal MR images; same patient. a: Preoperative MR image demonstrating cranio-caudal extension of the epidural collection, limited to the L4–5 interspace (*arrows*). b: Postoperative MR image obtained at the 3-week follow-up review documenting the surgical access point and areas of nonspecific and inhomogeneous contrast enhancement (*arrows*), despite the patient's clinical improvement.

eral agreement that a close collaboration between the hematologist and the surgeon may provide guidelines for therapy in such cases, giving these patients the possibility of survival and the opportunity to continue the treatment planned for the primary disease.

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