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Diagnosis of chronic osteomyelitis complicated with mycotic infection

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Introduction In the last decade, there has been an increase in the incidence rate of mycoses in patients after injuries and/or operations performed on limb segments and major joints. Mycoses are difficult to diagnose early because the mycotic flora may mimic the bacterial flora being present in the osteomyelitic nidus and primarily identified in the wound exudate. **Objective** To develop diagnostic criteria for osteomyelitis complicated with mycotic infection. **Methods** We performed a retrospective study of 28 patients (17 males and 11 females) aged 21 to 76 years (49 ± 16 years) who were treated for purulent inflammatory lesions of bones and/or joints at the clinic of osteology infection between 2000 and 2018. **Results** Mycotic infection was pathomorphologically detected in the osteomyelitis nidus of all patients. Patients were treated according to the established protocol including radical sequestrectomy, diagnostic biopsy and postoperative administration of antimicrobial and antifungal therapy. **Discussion** The study allowed identification of several diagnostic criteria for osteomyelitis complicated by mycotic infection. Pathomorphological examination of surgical specimen from purulent inflammatory nidus was shown to be the keystone in diagnosis of osteomyelitis complicated with mycoses.

Keywords: osteomyelitis, mycotic infection, diagnosis of osteomyelitis of mycotic etiology

INTRODUCTION

Treatment of chronic osteomyelitis remains a clinical challenge [1, 2, 3]. Trauma-induced osteomyelitis remains the most common cause with infection rates in open long bone fractures ranging between 5.3 and 75.4 % [1, 2]. Osteomyelitis can be associated with the iatrogenic introduction of infection due to inappropriate surgical options used to repair the injured bone. The risk of infection following IM nailing and plating is reported to range between 5 % and 17 % [1–4]. On the other hand, prosthetic joint infections represent a relatively new entity of chronic osteomyelitis. Their incidence is reported to be as high as 1 % to 4 % [5]. The standard treatment of chronic osteomyelitis involves thorough debridement of infected bone, options to retain or remove the infected implant and replace it with different hardware, and systemic antibiotic administration [1, 5, 6, 7]. Often patients with chronic osteomyelitis receive prolonged antibiotic therapy with high doses rather than debridement for removal of all infective and necrotic material [2, 3]. Antibiotics might need to be replaced in some cases when antimicrobial therapy starts before cultures have been obtained, usually at the time of debridement [1, 2, 3, 5, 6, 7].

Although all types of organisms may cause osteomyelitis bone infections are commonly caused by certain bacterial flora. In the last decade, there has been an increase in the incidence rate of mycoses in patients after injuries and/or operations performed on limb segments and major joints [9–17]. Mycoses are difficult to diagnose early [8–17]. The mycotic flora may mimic the bacterial flora being present in the osteomyelitic nidus and primarily identified in the wound exudate. This results in prolonged antibiotic therapy without use of antifungal medicines and finally leads to repeated revision procedures [9–17]. Such a continuous inadequate treatment can reduce immune system response, promote growth of persistent bacterial strains and spread of fungal infection. Therefore, early diagnosis of mycotic infection is important for optimizing treatment outcomes of chronic osteomyelitis.

Objective The purpose of the study was to develop diagnostic criteria for osteomyelitis complicated with mycotic infection.

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MATERIAL AND METHODS

We performed a retrospective study of 28 patients (17 males and 11 females) aged 21 to 76 years (49 ± 16 years) who were treated for purulent inflammatory lesions of bones and/or joints at the clinic of osteology infection between 2000 and 2018. The study was performed in accordance with ethical principles for medical research involving human subjects stated in the Declaration of Helsinki developed by the World Medical Association as revised in 2013. Written informed consent was obtained from all patients for publication of the findings without identifying details.

Preoperative radiological examination was performed for all patients using RADIOTEX radiography system, registration certificate FS № 2006/527; RAYMAT ASI, registration certificate FS № 2006/2099; CLINOMAT, registration certificate FS № 2006/559. Preoperative ultrasound was produced for 16 patients using AVISUS Hitachi ultrasound scanning system (Japan) and 7.5 MHz linear transducer. Duplex scanning provided images of vessels, measurement of blood flow velocity and spectrum analysis. An area of metatarsal metaphysis was referred to as a control (AP = 210 ± 10 CU).

Intraoperative wound sampling was performed for microbiological studies. Nutrient agar containing 5 % of blood, egg-yolk salt agar, Levine medium, Sabouraud agar growth medium were used to cultivate aerobic and facultative anaerobic bacteria. Cultures grew at 37˚C for 24-48 hours. Bacterial counts in clinical isolates were measured using solid agar culture media in accordance with procedural guidelines using decimal logarithm of evolved colonies (CFC/mL). Bacterial cultures were generically and specifically identified with conventional techniques to explore their tinctorial, cultural and biochemical characteristics, and ATB Expression Bacteriology analyzers (Bio Merieux, France), Walk Away 40 Automated Microbiology Assay System (USA) and WHONET 5.6 Microbiology laboratory database software [19]. Involved bone fragments, sequesters and the skin excised during surgical debridement were histologically examined. Specimen were fixed in neutral buffered formalin, decalcified and embedded in paraffin. Histological preparations (paraffin sections of 5-7 mcm cut with Reichard sledge microtome (Germany) were stained with hematoxylin and eosin, Pappenheim method and periodic acid Schiff for neutral mucopolysaccharides. Images of micropreparations were acquired with AxioCam digital camera, AxioScope.A1 microscope and Zen blue software (Carl Zeiss MicroImaging GmbH, Germany).

RESULTS

An injury to a limb and/or surgical intervention performed on one or several segments complicated with purulent infection was reported in medical records of all patients. Average infection duration was 11 years (range, 1-44 years). Patients received repeated courses of antimicrobial therapy, local treatment and several patients underwent 1 to 4 debridement interventions (Table 1).

Patients presented with disturbed supportability of a limb, wounds and/or sinuses on admission. Localization of necrotic foci is presented in Table 2. Some patients experienced long periods of high body temperature.

Physical examination of the patients revealed postoperative and/or posttraumatic scars, functioning wounds, ulcers and/or sinuses. Some patients had swollen soft tissues, cyanosis of the skin, disturbed capillary refill and weak arterial pulse wave (Table 3).

Ultrasound evaluation showed stenosis of major vessels at different levels (n = 4), weak magistral blood flow and open collaterals (n = 9), and no changes in hemodynamics revealed in three cases. Onychomycosis was diagnosed in all patients with disturbed magistral blood flow (n = 13) (Table 3). All patients had comorbid diseases with cardiovascular, gastrointestinal, urinogenital and spinal cord injuries being most common (Table 4).

Table 1

Treatment performed for patients with chronic osteomyelitis prior to admission to the Clinic of Osteology Infection

Number and type of surgeries performed prior to admission to the Clinic of Osteology Infection		Antimicrobial therapy received by the patients prior to admission to the Clinic of Osteology Infection
Type of intervention	Number of observations	
Orthopaedic procedure	19	13
Sequestrectomy	9	9

Table 2

Localization of necrotic focus

Localization of necrotic nidus	Number of patients
Foot	10
Femur	6
Tibia	1
Hip joint (periprosthetic joint infection)	4
Knee joint (periprosthetic joint infection)	3
Pelvis, spine (sacrum)	3
Clavicle	1

Table 3

Physical examination of patients

Physical findings	Number of observations
Wounds/ulcers	12
Sinuses	18
Lacerations	9
Scars	19
Hyperkeratosis	9
Edema	11
Hyperemia, cyanosis, paleness	3
Psoriatic plaques	1
Positive capillary refill test	3
Weak pulse in major vessels	22
Onychomycosis	13

Immune related diseases were diagnosed in 10 patients (34 %) who underwent immunosuppresive therapy. Radiographic examination of the majority of patients showed bone destruction (osteolysis), bone sequesters, periostitis, exostoses and sclerosis (Table 5). Foreign bodies (implants) could be visualized the articular cavity in cases of deep periprosthetic joint infection along with periostitis and bone defects. Arthritis of adjacent joints could be seen in patients with infection localized in the metaphyses (Table 5).

Preoperative laboratory blood tests showed signs of inflammation with leukocytosis, neurophilic imbalance, accelerated erythrocyte sedimentation rate, elevated C-reactive protein level (Table 6).

Table 4

Comorbid conditions in patients with chronic osteomyelitis

Comorbidities	Number of observations
Hypertension	12
CAD. Coronary artery disease, CHF	2
Congenital angiodysplasia (Parkes-Weber-Rubashov syndrome)	1
Anemia	5
Lower extremity varicose vein disease, CVI	1
PUD, duodenal ulcer, gastritis	3
Drug-induced liver injury with minimally decreased function	1
Chronic colitis	1
DM	2
Obesity	2
TSCI, flaccid lower paraplegia. Pelvic floor dysfunction	5
Chronic prostatitis	1
Bladder stone disease	2
Chronic pyelonephritis	3
Hypoplastic kidneys	2
Chronic bronchitis, remission, fungi	3
U.R.I.	1
Chronic hepatitis C	3
Hepatitis B	1
Chronic herpes virus infection, latent period. CMV, toxoplasmosis	1
HIV	1
Psoriasis	1
Osteogenic sarcoma	1
Breast cancer (left side) following operative and Rg treatment. Lymphostasis of the left upper limb	1

Table 5

Characteristic radiological picture in patients with chronic osteomyelitis

Radiographic manifestations	Number of observations
Osteolysis/destruction/osteoporosis	19
Osteophytes, exostoses	15
Osteolysis/sequestrum	7
Periosteal reaction	15
Changes in articular surfaces	4
Bone cysts, cavities	3
Osteosclerosis	13
Foreign bodies (implants)	8

Table 6

Laboratory blood tests in patients with chronic osteomyelitis

Inflammation markers		
Blood parameter	% of increase (n)	Median (range)
WBC (/mm^3) (WBC)	> 10.000/mm^3; 45 % (n = 28)	9.270 (100–37.000)
PMNs (%) (neutrophils)	> 80 %; 30 % (n = 28)	79.3 (10.3–90)
ESR (mm/h)	> 15 mm/hr; 96 % (n = 28)	86 (10–148)
CRP (mg/dl)	> 1 mg/dL; 100 % (n = 28)	51.5 (1.5–151)

The majority of the patients underwent one and more operative interventions and received repeated courses of antimicrobial therapy, so we examined perioperative biopsy samples taken from infection nidus to identify microflora. In addition to that, perioperative biopsies were obtained to detect mycotic infection, and fungal colonization of *Candida* species was isolated from specimen of 3 cases out of 28. Types of pathogens cultured are presented in Table 7. *Staphylococcus aureus*, *S. epidermidis*, Pseudomonas aeruginosa were shown to be most common organisms causing osteomyelitis, whereas other atypical organisms were identified as monocultures and microbial associations less frequently.

Pathohistological examination of biopsy samples and operation material taken from the involved sites showed signs of mycotic microflora with yeast-like cells and pseudomicellar structures seen in the specimen (Fig. 1).

Inflammatory reaction was identified in both infiltration and production forms depending on the type of organism. All patients with chronic osteomyelitis were treated according to the established protocol with reference to individual clinical manifestations. Radical sequestrnecrectomy and biopsy sampling were produced in all cases. Ilizarov bone fixation (n = 13) was performed and cemented spaces implanted (n = 7). All patients received etiotropic antimicrobial therapy administered postoperatively for 2-4 weeks. With pathomorphological findings available all patient were administered additional antifungal therapy including itrakonazole (n = 10), fluconazole (n = 14), amphotericin B (n = 4). Ilizarov bone transport was produced to repair bone defect (n = 3) with purulent infection arrested. Despite the treatments performed (Table 8) two patients developed recurrent osteomyelitis at one-year follow-up. Recurrence was observed at 1 to 3 years in 13 patients. And 3 patients had a recurrence at 3 years and over. The recurrences were treated with radical debridement, antimicrobial and antifungal therapies. Persistent quiescence was postoperatively achieved in all patients.

Table 7

Microflora of mycotic etiology detected in patients with chronic osteomyelitis

Types of pathogen		Number of observations
Gram-positive bacteria	*Staphylococcus aureus*	15
	Staphylococcus epidermidis	8
	Staphilococcus hominis subsp	1
	Staphylococcus saprophyticus	2
	Staphylococcus haemolyticus	1
	Streptococcus pyogenes	1
	Bacillus spp.	1
	Actinomycos spp.	1
	Enterococus faecalis	6
	Corynebacterium spp.	2
Gram-negative bacteria	*Myroides sp.*	1
	Stenotrophomonas maltophilia	1
	Enterobacter cloacae	3
	Pseudomonas aeruginosa	15
	Alcaligenes sp.	3
	Leuconostoc sp.	1
	Escherichia coli	8
	Proteus mirabilis	7
	Achromobacter xilosoxidans	1
	Klebsiella pneumoniae	3
Fungi	*Candida spp.*	3

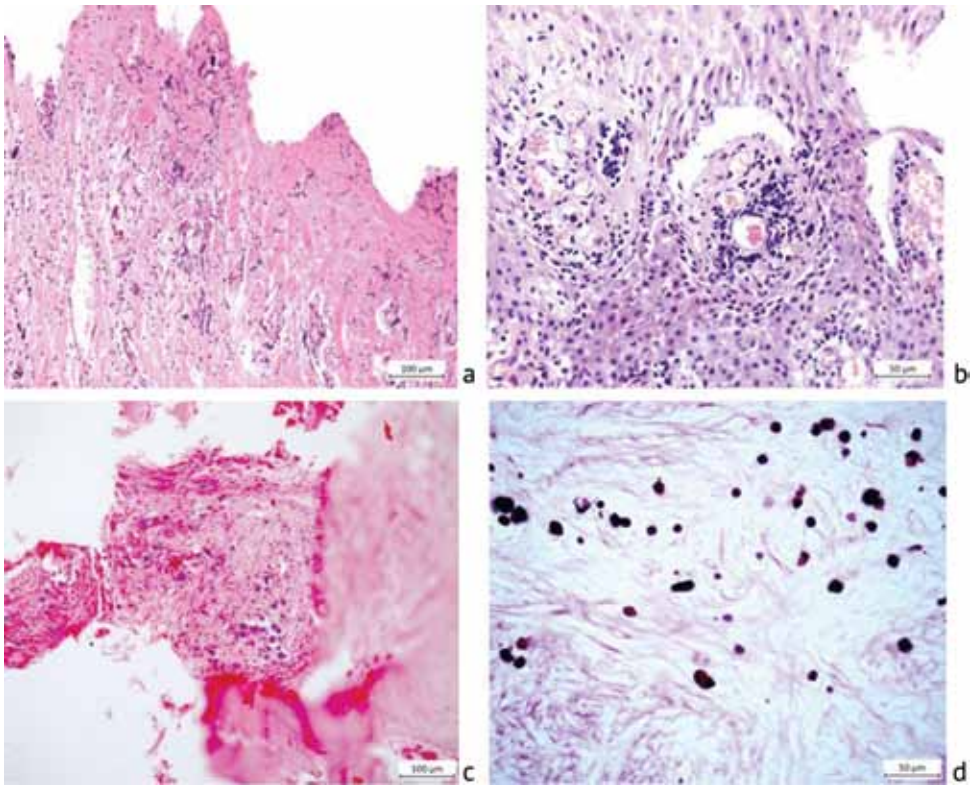

Fig. 1 Signs of mycotic process in the specimen (***a***) seen at the edge of the defect, pseudomicelium net, (***b***) yeast-like flora, (***c, d***) blastomycosis, yeast-like cells at the site of productive inflammation. Magnification: (***a, c***) ×250; (***b, d***) ×500. Stained with hematoxylin&eosin (***a***), Pappenheim method (***b, c***), periodic acid Schiff (***d***)

Table 8

Long-term follow-ups of patients with chronic osteomyelitis

Follow-up	Quiescence	Recurrence
Up to one year	26	2
1–3 years	15	13
3 years and over	25	3

DISCUSSION

Our series allowed identification of several diagnostic criteria for osteomyelitis complicated with mycotic infection. In our opinion and according to M.N. Gamaletsou et al. (2014), L.C. Ferreira, (2016), R. Clemence et al. (2017), chronic purulent inflammation process, repeated courses of antimicrobial therapy and operative interventions reported in medical history of a patient can be considered as one of causative factors and diagnostic criteria for chronic osteomyelitis [9–17]. Decrease in blood supply plays a role in the development of mycosis. C. Richaud et al. (2017) reported a series of 28 patients with mycosis who developed ischemia of the involved limb in most of the cases. Immunosuppression from hormone, chemotherapeutic agents used for oncologic and autoimmune diseases, hemodialysis and organ transplantation is a risk factor for mycosis. Immunodeficiency caused by HIV is another contributing factor [11–17]. The studies performed by the International Working Group on the Diabetic Foot showed that mycosis was detected along with bacterial flora in some diabetic patients [18]. Osteolysis combined with excessive periosteal reaction was shown to be the principal radiological criteria for diagnosis of chronic osteomyelitis in mycotic patients (Jain R., 2014). However, the above radiological manifestations are likely to be an indication of metaplastic process [11, 14, 15, 16].

In our opinion and according to Cohen S.H. et al. (2010), Jain R. et al. (2014), Gamaletsou M.N. et al. (2014) microbial flora being present at the site of purulent inflammation as low pathogenic organisms of monoinfection and microbial associations can be one of manifestations of mycotic infection in the

nidus. The series reported by Cohen S.H. et al. (2010), Jain R. et al. (2014), Gamaletsou M.N. et al. (2014) analyzed dynamics in microbial flora in osteomyelitic focus of mycotic patients and revealed pathogenic flora being replaced with conventionally pathogenic flora due to mycotic invasion [11, 14, 15, 16]. Pathomorphological examination of biopsy sample at the nidus of purulent infection is the basic diagnostic criterion. Diagnostic biopsy can be produced as part of preoperative preparation of the patient [9–17]. Risk grading scale for mycosis was developed with the above factors in mind marking presence/absence of the signs in the right-hand column (Table 9).

With 50 % positive answers diagnostic biopsy at the site of purulent inflammation can be recommended as part of preoperative preparation.

Table 9

Risk grading scale for mycosis in osteomyelitic nidus

Diagnostic criterion	+/-
Long-term history of the disease	
Immunosuppression, diabetes mellitus	
Radiologically: non-specific osteolysis, periosteal reaction	
Microbiologically atypical microflora	
Angiopathy, ischemia of the limb	
Extensive scars of soft tissues of the involved limb	

CONCLUSION

1. Unfavorable course of purulent infection (duration, recurrence, atypical clinical manifestations, multiple failures in antimicrobial therapy) necessitates additional diagnostic procedures and their adequate assessment.

2. Success of positive outcomes with mycosis and osteomyelitis relies on adequate diagnosis providing a complex approach to radical surgical debridement and targeted etiotropic antimicrobial and antifungal therapy.

3. With high risk of mycosis identified at the osteomyelitic nidus biopsy sampling is practical.

4. Pathomorphological examination of biopsy sample is the basic diagnostic criterion.

5. Possibilities with successful treatment of mycosis have been extended due to effective and safe antifungal agents being available in recent years.

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