Possibilities with differential diagnosis of hematogenous osteomyelitis and malignant bone tumour

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Introduction Hematogenous osteomyelitis and malignant bone tumours are not rare and present a clinical and radiological variety of bone changes. Morphological patterns can be studied at large institutions having relevant medical facilities for the diagnosis of bone lesions. Despite the advanced technologies of recent decades used to verify the pathological conditions differential diagnosis of infectious diseases and malignant bone tumors is still a problem for medical science and practice. **Material and methods** The study included 96 patients with hematogenous osteomyelitis and 31 patients with malignant bone tumour characterised by atypical clinical manifestations that required differential diagnosis. A. Wald's consecutive analysis was used to compare the findings of clinical, laboratory and instrumental examinations. **Results** Mathematical model for differential diagnosis of hematogenous osteomyelitis and malignant bone tumour was developed with database of 127 patients. 13 differential diagnostic criteria were identified and quantified including patients' gender, age, comorbidities, localisation of the pathological process, results of laboratory tests, etc. An algorithm for differential diagnosis of hematogenous osteomyelitis and malignant bone tumour was devised. Immune parameters in blood of 63 patients were evaluated with prognostic purposes. **Conclusion** Practical evaluation of differential diagnosis of hematogenous osteomyelitis and malignant bone tumour showed accuracy of primary diagnosis of 89.2 % at outpatient phase and 91.6 % in the retrospective group that resulted in a reduced workup procedure and referral to a tertiary hospital.
Keywords: hematogenous osteomyelitis, malignant bone tumor, differential diagnosis

INTRODUCTION

Hematogenous osteomyelitis (HO) has long been known to be a surgical problem. The incidence has remained relatively stable and HO accounts for 14.8 to 28.8 % of all cases of osteomyelitis [1, 2, 3]. Diagnosis of HO is not difficult with evident clinical presentation. Unfortunately, sometimes HO causes no signs or symptoms with atypical laboratory tests and results of radiography being equivocal and too nonspecific to allow a diagnosis to be reached [4, 5, 6]. Identification of the causative microorganisms is essential for treatment [7]. This can be problematic with outpatient medical care and at the hospitals located far from regional administrative centres [8].

Differential diagnosis between bone infection including HO and bone tumours that are not rare is important to distinguish osteomyelitis from malignant lesions that can occur at early childhood and elderly people when the clinical context does not discriminate

between these [9, 10, 11]. This confusion can lead to delays in treatment, inadequate management and poor outcomes [12].

There is a steady increase in publications on differential diagnosis between osteomyelitis and bone tumours seen in recent years [11, 13, 14, 15, 16]. They are mostly descriptive and the data of the practical application are controversial. There is no consensus regarding types and importance of differential diagnosis criteria. Study of aspects related to differential diagnosis between hematogenous osteomyelitis and malignant bone tumours can be relevant for scientific medical investigations.

The purpose of this study was to identify diagnostic criteria for hematogenous osteomyelitis and malignant bone tumours, produce the quantitative assessment and devise mathematical representation of differential diagnosis.

MATERIAL AND METHODS

The study was approved by the institutional review board of North-West Mechnikov State Medical University and conducted in accordance

with Declaration of Helsinki "Ethical principles for medical research involving human subjects" as amended in 2000 and "Guidelines for medical

practice in the Russian Federation" regulated by Decree № 266 dtd 19.06.2003 Minzdrava RF.

There were three inclusion criteria of the retrospective prospective cohort clinical study: 1) cases when both diagnoses were suspected and differential diagnosis required, observations with mismatched primary and final diagnoses of either HO or malignant bone tumour (MBT); 2) time period between 2016 and 2017; 3) place (hospital). Cases with classical clinical presentation, typical radiological manifestations and laboratory tests that required no differential diagnosis were excluded from the study.

A model of differential diagnosis between HO and MBT included factors having statistically significant ($p < 0.05$) association with provisional diagnosis and also factors having statistically reported significance for provisional diagnosis. Significance level was determined with MedCalc software version 18.2.1.

Two subgroups were identified in retrospective group including 96 HO patients and 35 MBT cases. The two subgroups of retrospective study were compared using A.Wald's (1945) sequential analysis modified by E.V.Gubler and A.A.Genkin (1973) [17, 18] to determine criteria of differential diagnosis and the quantitative equivalent. The model of differential diagnosis between HO and MBT was created using rating values at risk of a pathological condition caused by infection or malignancy detected retrospectively.

Decision making relied on the total index of differential diagnosis compared with threshold values calculated using formulas:

$$\text{threshold A} = 10 \times \ln((1-\alpha)/\beta),$$
$$\text{threshold B} = 10 \times \ln(\alpha/(1-\beta)),$$

where α and β are type I and type II errors [12]. False diagnosis of MBT with intrinsically detected HO in a case was accepted as type I error α. False diagnosis of HO with intrinsically detected MBT in a case was accepted as type II error β. Values α and β were established as equal to 0.2 (20 %).

Sensitivity (Se) and specificity (Sp) were determined to evaluate the efficacy of differential diagnosis model as well as diagnostic accuracy, positive and negative prognostic value of the test using MedCalc software version 18.2.1.

There were 213 HO and MBT patients treated at a trauma and orthopaedics clinic and clinical facilities of the department of trauma, orthopaedics and field surgery, North-West Mechnikov State Medical University (hereinafter clinic) between 2016 and 2017. From them, 159 patients were diagnosed with HO, and 34 with MBT. Evident clinical presentation, radiological manifestations and laboratory tests being typical for HO were detected in 63 (39.6 %) out of 159 patients with no need of differential diagnosis. The 63 observations were excluded from the study.

MBT was definitely diagnosed in 23 (42.6 %) cases out of 54 malignant patients. Metastatic bone tumours were detected in all the observations with histologically confirmed primary cancer of different localisation. The study included 31 MBT patients who required differential diagnosis of other pathological conditions.

127 participants, 96 HO and 31 MBT patients, were recruited for the study. Those were the cases that required more diagnostic procedures to make a final diagnosis. Comparative analysis of clinical, laboratory, radiographic and immune findings was conducted in patients of the two groups identifying criteria of differential diagnosis and the quantitative equivalent.

Effectiveness of the technique developed was evaluated in 148 patients in 2017. Among them there were 87 inpatients and 61 outpatients seen at outpatient hospitals of Saint Petersburg and Leningradskaya oblast, municipal outpatient hospitals № 38 and № 120, Lomonosovskaya regional hospital, 38 occupational health facilities FMBA of Russia.

Hematological parameters were determined using automated flow cytometry with "CytoDiff®" reagents to detect laboratory markers of differential diagnosis between HO and MBT with Cytomics FC500 flow cytometer (Beckman Coulter, USA). The test involves the capability of specific monoclonal antibodies to bind with antigen determinants and identifies white blood cells differentiating 14 hematological parameters including total leukocyte count, lymphocytes, B-lymphocytes, T-lymphocytes/NK (activated and non-activated T-NK-cells), inflammatory and non-inflammatory monocytes, mature segmented neutrophils, immature granulocytes, eosinophils and basophils. The result is recorded as the percentage of positive staining cells. The use of total leukocyte count measured with automated hematology analyser allows for obtaining absolute content of cell populations in assay.

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RESULTS

The review of 76 parameters describing patient's condition, his/her objective, laboratory and instrumental findings was produced to include general and local status of the patient, gender, age, comorbidities, body mass index, etc. Particular laboratory and instrumental tests were analysed. Parameters used for differential diagnosis between HO and MBT comprised 14 criteria. The data on distribution of HO and MBT patients with regard to localisation of pathological process as one of differential diagnosis criteria are presented in Table 1.

As seen from Table 1 HO group showed 78 % involvement of long bones while pathologic process was localised in cancellous bone in 55 % of MBT patients. Statistical analysis exhibited 3 degrees of freedom and χ^2 measured 12.126. Critical χ^2 was 11.345 with significance level at $p < 0.01$. Correlation between factorial and resultant characteristics was statistically significant with significance level at $p < 0.01$. The type of involved bone was recognised for mathematical model of differential diagnosis. Other criteria were selected in a similar manner.

Correlation index and prognosis coefficient were calculated with full list of relevant factors identified for differential diagnosis. Correlation index was defined as a ratio between the incidence of an attribute in HO group and the incidence of the attribute in MBT. Prognosis coefficient was defined as the natural logarithm (ln) of correlation index multiplied by 10 for easier calculations. The resultant prognosis coefficient was «+3.5» in involved long bones, «–7.9» in involved cancellous bone, «–7.4» in spine and «–4.2» in other bones. Long bone involvement allowed us to suspect the greater probability of HO. Then all prognosis coefficients calculated were summarised and the resultant presented a cumulative prognosis index (PI). PI was calculated at different stages of examination and treatment with confidence interval ranging from «–14» to «+14» conventional units (CU). If the cumulative PI was «+14» CU and over the probability of HO was more than 80 %. The cumulative PI of less than «–14» CU showed the similar probability of MBT. Diagnosis was ambiguous for the reliability target with cumulative PI ranging from «–14» to «+14» CU. Full list of prognostic criteria and indexes calculated for differential diagnosis is presented in Table 2.

Table 1

Distribution of HO and MBT patients with regard to localisation of pathological process

| Localisation | Number of observations | | | |
| | HO (n = 96) | | MBT (n = 31) | |
	abs.	%	abs.	%
Long bones	75	78.1	17	54.8
Cancellous bone	14	14.6	10	32.3
Spine	3	3.1	2	6.5
Others (ribs, clavicle)	4	4.2	2	6.4
TOTAL	96	100.0	31	100.0

Table 2

Structure of criteria used for differential diagnosis between HO and MBT

| Prognostic criteria | Number of patients (%) | | Correlation index | Prognosis coefficient |
	HO	MBT		
1. Gender:				
Male	77	42	1.833	6.1
Female	23	58	0.397	-9.2
2. Age, years:				
18–29	6	32	0.188	-16.7
30–44	27	16	1.688	5.2
45–59	40	26	1.538	4.3
60–74	26	26	1.000	0
75–89	1	–	–	–

Continuation of table 2

Structure of criteria used for differential diagnosis between HO and MBT

Prognostic criteria	Number of patients (%)		Correlation index	Prognosis coefficient
	HO	MBT		
3. Ability to work:				
maintained	72	48	1.500	4.1
retired	28	52	0.538	-6.2
4. Pulmonary comorbidity				
COPD diagnosed	6	16	0.375	-9.8
no COPD	94	84	1.119	1.1
5. Cardiovascular comorbidity				
IHD, HBP diagnosed	51	16	3.188	11.6
no IHD, HBP	49	84	0.583	-5.4
6. Gastrointestinal comorbidity				
present	45	26	1.731	5.5
absent	55	74	0.743	-3.0
7. Renal excretory function				
chronic pyelonephritis diagnosed	12	6	2.000	6.9
no chronic pyelonephritis	88	94	0.936	-0.7
8. Trauma in the history				
reported	35	10	3.500	12.5
not reported	65	90	0.722	-3.3
9. Viral hepatitis				
reported	12	6	2.000	6.9
not reported	88	94	0.936	-0.7
10. Drug and food allergies				
present	20	10	2.000	6.9
absent	80	90	0.889	-1.2
11. Location of pathological process				
upper limb	14	39	0.359	-11.2
lower limb	81	55	1.473	3.9
other	5	6	0.833	-1.8
12. Type of involved bone				
long bone	78	55	1.418	3.5
cancellous bone	15	32	0.469	-7.9
spine	3	7	0.429	-7.4
others	4	6	0.667	-4.2
13. Blood groups				
0 (I)	32	32	1.000	0
A (II)	27	36	0.750	-2.9
B (III)	22	13	1.692	5.3
AB (IV)	7	10	0.700	-3.6
14. Sinuses				
reported	82	13	6.308	18.4
not reported	18	87	0.207	-15.8

Development and introduction of objective diagnostic techniques using laboratory tests have greatly accelerated over the past decades. With flow cytometry several new hematological tests have been made available as screening tools [19, 20, 21]. The tests were performed for 63 patients of the prospective group including 34 HO and 29 MBT patients (Table 3).

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Table 3

Counting mean numbers of specific leukocyte subpopulations in patients with HO and MBT

Leukocyte populations	Me (C25-C75) × 10⁹/L (norm)	HO (n = 34)	MBT (n = 29)	p-level HO vs MBT
Total leukocyte count	(6.4–7.6)	7.4 (6.3–8.6)	7.3 (5.7–8.9)	0.6147
B- lymphocytes (CD19+)	(0.186–0.258)	0.310* (0.170–0.438)	0.136 (0.039–0.298)	0.0001
CD16 negative T-lymphocytes and NK-cells (non-activated)	(1.418–1.870)	1.881* (1.545–2.178)	1.303 (1.038–1.614)	0.0076
CD16 positive T-lymphocytes and NK-cells (activated)	(0.188–0.482)	0.338* (0.178–0.446)	0.197 (0.137–0.303)	0.0020
Total T-lymphocytes count and NK-cells	(1.566–2.301)	2.290* (1.756–2.573)	1.547 (1.104–1.933)	0.0028
Total lymphocyte count	(1.696–2.463)	2.725* (2.102–3.214)	1.676 (1.312–2.107)	0.00003
CD16 negative monocytes	(0.451–0.579)	0.590 (0.444–0.740)	0.548 (0.411–0.757)	0.7028
CD16 positive monocytes (proinflammatory)	(0.026–0.059)	0.037 (0.026–0.048)	0.038 (0.027–0.053)	0.5728
Total monocyte count	(0.495–0.651)	0.618 (0.480–0.781)	0.595 (0.453–0.784)	0.7695
CD16 negative immature granulocytes (neutrophils)	(0.002–0.010)	0.007 (0.003–0.011)	0.010* (0.005–0.052)	0.0290
Total eosinophil count	(0.091–0.269)	0.224* (0.162–0.381)	0.130 (0.084–0.238)	0.0006
CD16 positive mature granulocytes (neutrophils)	(3.473–4.659)	3.678 (2.969–4.589)	4.451 (3.095–6.056)	0.1976
Total granulocyte count (neutrophils)	(3.497–4.738)	3.687 (2.972–4.599)	4.475 (3.106–6.065)	0.1755
Total basophil count	(0.038–0.057)	0.056* (0.038–0.089)	0.042 (0.020–0.052)	0.0016

Note: * – p < 0.05

No statistically significant differences were found in total leukocyte count of HO and MBT cases. Statistically significant (p < 0.05) increase in absolute number of total leukocyte count was detected in HO group due to increase in B-lymphocyte, T/NK-lymphocyte as well as basophil and eosinophil count as compared to MBT patients. The changes are descriptive of specific immune response to infectious agent. There was statistically significant (p < 0.05) decrease in identical population count in whole blood of MBT patients due to the ability of cancer cells produce immunosuppression substances (transforming growth factor-β (TGF-β), interleukin-10), inhibitors of cytotoxicity, complement-inhibitory proteins, etc. Identical total leukocyte count in different types of bone pathology does not allow for adequate evaluation of immune system whereas changes in leukocyte subpopulation count have a distinct clinical significance for differential diagnosis between HO and MBT.

DISCUSSION

The validity of the diagnostic model/test was assessed with retrospective cohort study involving 131 participants. The findings showed high operating characteristics (95 % CI included in brackets) with sensitivity (Se) of 88.6 % (73.3 %; 96.8 %), specificity (Sp) of 92.7 % (85.5 %; 97.0 %), positive predictive value of 81.6 % (68.2 %; 90.1 %), negative predictive value of 95.7 % (89.8 %; 98.3 %) and diagnostic accuracy of 91.6 % (85.5 %; 95.7 %).

Prospective study performed at several hospitals of Saint Petersburg and Leningradskaya Oblast in 2017 included 148 patients who required differential diagnosis between HO and MBT. Operating characteristics of the diagnostic test in prospective study showed similar findings reported in retrospective study with sensitivity (Se) of 90.2 % (78.6 %; 96.8 %), specificity (Sp) of 88.7 % (80.6 %; 94.2 %), positive predictive value of 80.7 % (70.4 %; 88.0 %), negative predictive value of 94.5 % (88.2 %; 97.5 %) and diagnostic accuracy of 89.2 % (83.0 %; 93.7 %).

Questions of differential diagnosis between HO and MBT have been discussed in Russian and foreign literature since the 40-es of the last centuries [22, 23]. Although tremendous progress has been made in diagnosis of bone pathology using radiography, computed tomography and magnetic resonance imaging, immunological tests, morphological study the problem is still urgent in clinical medicine since it involves both organizational and technological

aspects. On the one hand, not all primary care hospitals are staffed with specialist who can perform adequate bone harvesting procedure, and osteomorphologists are available at major health care facilities. On the other hand, the patients often receive treatment at a non-core health care facility since HO and MBT must be treated at infection surgery and oncology departments, correspondingly, from legal point of view. And it takes longer to get accurate diagnosis.

The treatment tactics are conceptually different for HO and MBT and delayed verification of the diagnosis can result in lethal outcome in both cases.

The model offered for differential diagnosis with simple and accessible criteria facilitates provisional diagnosis to be made at preadmission phase, referrals of patients to a core health care facility and pathogenically substantiated treatment to be undertaken early for the best possible outcome.

CONCLUSION

Therefore, the usage of differential diagnosis between hematogenous osteomyelitis and malignant bone tumour in clinical settings showed accuracy of provisional diagnosis in 89.2 % to 91.6 % of the cases. Physicians were able to formulate conceptual framework of management within short period of time. Clinical testing of differential diagnosis between HO and MBT in patients of prospective group confirms adequate choice of criterion.

Criterion with maximum range of positive and negative prognosis coefficients were most important for tentative diagnosis of hematogenous osteomyelitis

including male gender, age over 30 years, an injury and sinuses reported in medical history.

Frequency of HO and MBT has not been reported to decrease. In recent years atypical clinical manifestations of the conditions have been verified. Early diagnosis including outpatient tests is essential for reduced workup and timely specialised medical assistance. Our findings showed that modern organisational approaches in patients with atypical clinical manifestations of bone infections and tumours allowed for improved outcomes due to early diagnosis and timely specialised medical assistance.

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