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PERIANAL INFECTIOUS COMPLICATIONS IN PATIENTS WITH GRANULOCYTOPENIA AND HAEMATOLOGICAL MALIGNANCIES

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AIM: to study the perianal infection (PI) in patients with granulocytopaenia (GCP) and hematological malignancies (HM).
PATIENTS AND METHODS: the prospective study (2016-1018) includes 95 episodes of PI in 76 patients with HM (male/female 35/44; mean age of 35 (17-69)). 43(54.4%) of the patients were detected to develop acute leukemia (AML – 34 (43%); ALL – 9(11.4%); NHL – 17(21.5%).
The comparison of PI episodes within the GCP period (number of granulocytes less than 0.5x10^9/l) and without it was done.
RESULTS: PI episodes within the period of GCP were significantly much more often than those without GCP (77.9% vs 22.1%, relative risk 3.5 (95% CI: 2.4-5.2).
The biggest number of PI episodes in the setting of GCP was registered within the period of chemotherapy (ChT): in the phase of consolidation (28.4%) and induction (13.3%) of acute leukemia ChT and lymphomas' ChT (20.3%).
Anal fissures were the most frequent source of PI within GCP period (66.2% vs 19.1% without GCP, p<0.001).
Inflammatory changes in perianal tissues were clinical features of PI in the setting of GCP in 89.2% of the cases: inflammatory mass in 71.6% (vs 23.8% without GCP, p<0.001), abscess in 8.1% (vs 66.7% without GCP, p<0.001).
In 10.8% of the cases of PI with GCP only perianal pain and fever were registered. No tissues change was detected with the lowest WBC count (Me 0.2 (0.1-0.5) x10^9/l). Bloodstream infections were detected in 15 (20.3%) episodes within the period of GCP only, of them in 6 (8.1%) cases the species matching of microorganisms in blood and in rectum was noticed.
Within the period of GCP antibacterial therapy was carried out in 98.6% of the cases: antibacterial therapy alone was applied in 87.8% of the episodes (vs 7.2% without GCP, p<0.001); both antibacterial therapy and surgical treatment were carried out in 10.8% (vs 61.9% without GCP, p<0.001) of the cases. Mean duration of antibiotic treatment of patients with GCP was drastically longer in the group of postoperative patients in comparison with the group of those who had conservative treatment (25.5 vs 15.1 days, p=0.05). Antimicrobial therapy within GCP period resulted into inflammation regress in 83.1% of the cases; abscess or fistula formation, hence surgical treatment in 13.8% of the cases; progression of infection in 3.1% of the cases. Increase of GCP duration up to 30 and more days is connected with bacteremia rate increase (12.5% vs 28%, p<0.05); combinations of PI with other infections (25% vs 52%, p<0.05); requirement of antimicrobial therapy modification (16.7% vs 40%, p<0.05).
CONCLUSION: GCP significantly raises risk of PI. PI that develops in the setting of GCP, is characterized by abnormal, often low clinical manifestations and high risk of sepsis.
Invasion of microorganisms through affected tissue seals is the basic mechanism of perianalinfection within the period of GCP. Antibacterial therapy is the prior method of PI treatment in the settings of GCP; antibacterial therapy efficiency is 83.1%. Need for surgery in the period of GCP is associated with the infectious episode and antibacterial therapy duration increase. Lengthening of GCP is a negative predictor in PI treatment.

[Key words: perinatal infection, abscess, leukemia, agranulocytosis, granulocytopaenia, neutropenia, hemoblastosis]

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LIST OF ABBREVIATIONS

AA – aplastic anemia
BLES - extended-spectrum β-lactamases
GCP – ranulocytopenia
MM – multiple myeloma
MRI - magnetic resonance imaging
ALL – acute lymphoblastic leukemia
AML – acute myeloid leukemia
PI – perianal infection
CT – chemotherapy

INTRODUCTION

The leading factor in the development of infectious complications in oncohematology is granulocytopenia (GCP). The rate of infectious complications increases with a decrease in the number of granulocytes less than $1.0x10^9$/l, and significantly increases with granulocytes less than $0.5x10^9$/l. Under these conditions, microorganisms that colonize the mucous membranes and are not pathogenic can penetrate damaged tissue barriers and cause infections, including bacteremia [1].

GCP can be either a manifestation of the hematological disease itself, or a consequence of antitumor therapy. The frequency of infectious lesions of perianal tissues in oncohematological patients during GCP reaches 10.8% [2].

The absence of granulocytes significantly changes not only the occurrence, but also the clinical manifestations of infectious processes. The formation of inflammatory changes in tissues may be delayed and have atypical forms.

To describe infections in the perianal area in such patients, the term "anorectal" or "perianal infection" (PI) is used, which includes both perianal abscesses and fistulas, as well as other clinical forms, such as inflammatory mass, ulceration, necrosis, soft tissue damage due to the hematogenic spread of infection, etc. [3-9].

A peculiar feature of infectious processes occurring against the background of GCP is a combination of a poor clinical signs and local manifestations with a high frequency of sepsis and mortality [1].

Anoanal pain may be the only symptom of PI in patients with severe GCP [3]. The proportion of infectious complications that occur without a significant increase in body temperature in patients with oncohematological diseases receiving modern chemotherapy (CT) is 20-28% [1-3], especially often infectious processes without fever are observed against the background of steroid therapy.

Sepsis is registered in 20-33% of patients with PI and GCP [9,10]. PI is one of the causes of septic shock in patients with neutropenia [5,9].

Publications in the 1980s and 1990s showed a high mortality rate among patients with PI and GCP, reaching 50% [3, 11]. In recent studies, the mortality rate associated with PI does not exceed 5% [2,5,7,10,16]. The authors attribute the decrease in mortality to early diagnosis and early initiation of antimicrobial therapy, the use of stimulating factor colonies to reduce the duration of GCP [7].

Understanding the features of the infectious process in perianal tissues in patients with GCP, factors that determine the prognosis is necessary to determine the optimal approach and successful treatment.

AIM

To study the features of perianal infection (PI) in patients with granulocytopenia (GCP) and tumor diseases of the blood system.

PATIENTS AND METHODS

The criteria for inclusion of patients in the study were: established diagnosis of hemoblastosis and the presence of PI signs. Patients were treated at the NMRC (the national medical research center)of Hematology (Moscow) from 2016 to 2018. We analyzed all the PI episodes for a given time period.

In accordance with the study protocol, a database was created, which included the following information: age, gender of the patient; diagnosis of hematological disease and stage of treatment; presence and duration of GCP; clinical manifestations of PI, duration of PI episode; treatment option; outcome of inflammation; data fromlaboratory and microbiological tests.

A severe degree of GCP was found with a decrease in the absolute number of granulocytes (neutrophils) less than $0.5x10^9$/l.

To analyze and identify the value of GCP, all the PI episodes were divided into two groups: the first group – episodes that developed against the background of severe GCP; the second one - without GCP.

The presence of inflammation signs of the perianal tissue was evaluated clinically based on the patient's complaints, the presence of fever, local signs of PI in

Table 1. *Characteristics of patients with perinatal infection (PI)*

Indicator	Number of patients, n(%)
Number of patients	79
Gender m/f	35/44
Agemedian (span) years	35(17-69)
Diagnosis	
Acute myeloid leukemia	34 (43)
Acute lymphoblastic leukemia	9 (11.4)
Non-Hodgkin'slymphomas	17(21.5)
Hodgkin's Lymphoma	6 (7.6)
Aplastic anemia	6 (7.6)
Multiple Myeloma	4 (5.1)
Others	3 (3.8)
Transferred from other hospitals	8(10.1)
Patients with 1 PI episode	67(84.8)
Patients with 2 PI episodes	8(10.1)
Patients with 3 PI episodes	4(5.1)

Table 2. *Indication of PI cases in patients with and without GCP*

Indicator	PI episodes, n (%)		p
	With GCP	Without GCP	
Number of PI episodes	**74**	**21**	
Connection with ChT:			
before the start of ChT	3(4.1)	6(28.6)	0,05
during ChT	55(74.3)	10(47.6)	
after the end of ChT	4(5.4)	4(19.0)	
ChT of acuteleukemia:	40(54.3)	7(33.3)	
induction	14(18.9)	4(19.0)	0.01
consolidation	21(28.3)	3(14.3)	
supportive therapy	5(6.8)	0	
Lymphoma ChT	15(20.3)	3(14.3)	
Allo-BMT	7(9.5)	0(0)	0.01
Auto-BMT (bone marrow transplantation)	5(6.8)	1(4.8)	
Remission of hemoblastosis	46(62.5)	10(47.6)	0.09
Combination of PI episode with other infections	32(43.2)	4(19.0)	0.05
Blood stream infections	15(20.3)	0(0)	0.01
Septic shock	2(2.7)	0(0)	0.60
Development of a PI episode on the background of antibacterial therapy	19(25.7)	0(0)	0.01
Clinical manifestations:			
abscess	6(8.1)	14(66.7)	<0.001
inflammatory mass	53(71.6)	5(23.8)	
necrosis/ulcers	7(9.5)	2(9.5)	
pain	8(10.8)	0(0)	
Source of infection:			
anal crypts	3(4.1)	7(33.3)	<0.001
anal fissure	49(66.2)	4(19.1)	
fistulas	10(13.5)	7(33.3)	
postoperative wound	2(2.7)	0	
others	10(13.5)	3(14.3)	

**Total of 95 PI episodes in 79 patients*

the form of edema, hyperemia, and pain in the perianal area. In case of a clinically unclear diagnosis, the examination data were supplemented with visualization using magnetic resonance imaging (MRI) or computed tomography (CT).

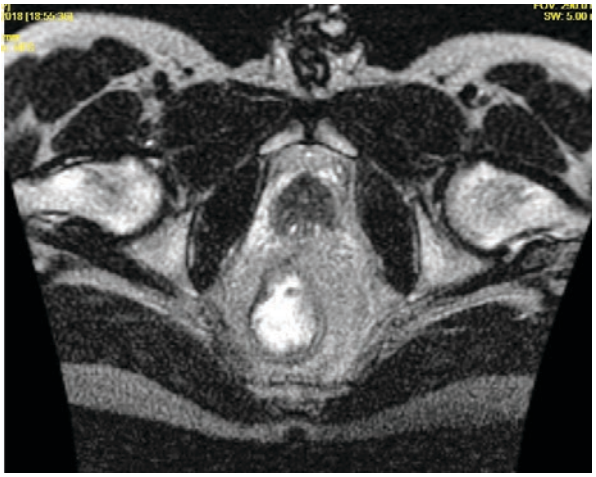

Figure 1. *Pelvic MRI. Patient P. Diagnosis: Acute Myeloid Leukemia, granulocytopenia. Pararectum edema*

MRI/CT signs of PI were the presence of cavities in the perianal tissues, fluid collections, defects in the anal wall and fistula tracts.

In patients with GCP, in the presence of clinical data, a sufficient MRI/CT sign of PI was considered to be the presence of edema of the perianaltissues. Sources of infection were evaluated separately based on examination or MRI / CT data.

Based on the data obtained, the clinical forms of PI were determined: abscess, inflammatory mass, or necrosis. In patients with severe GCP, the presence of pain in the perianal area and fever were considered sufficient signs of infection.

To identify the nature of the microflora, a microbiological test of smears from the anal mucosa was performed when the patient was admitted to the hospital, the test was repeated when the focus of infection was detected, and antimicrobial therapy was monitored.

At a temperature of more than 38°C, blood was taken

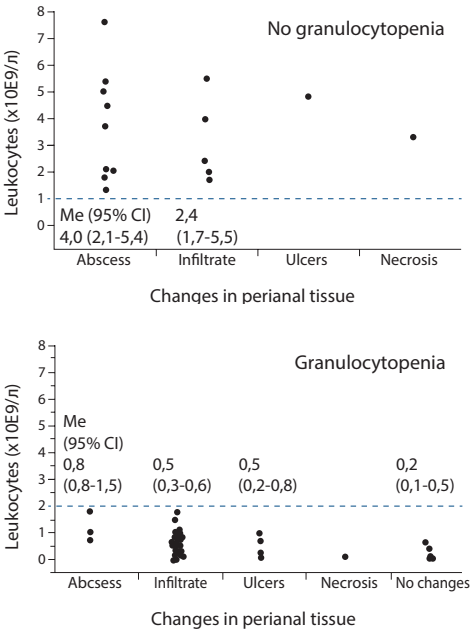

Figure 2. *Comparison of changes in perianal tissue in patients with perianal infection in the group with GCP (lower figure) and without GCP (upper figure). The highest level of white blood cells was observed in abscess (both in patients with GCP: median test, p=0.05, and in patients without GCP); the lowest level of white blood cells was observed in patients with PI who had no visible changes in the perianal tissue.*

from the vein and the hemoculture was examined.

When considering PI as a possible source of infection in sepsis, the type of microorganisms isolated from the rectum and blood was taken into account.

If PI was detected in patients with GCP, intravenous antibiotics were used. For initial antibacterial therapy, beta-lactam antibiotics with beta-lactamase inhibitors (piperacillin/tazobactam or cefoperazone/sulbactam) or carbapenem with anti-pseudomonas activity (imipenem/cilastin, meropenem, doripenem) were used. Modification of antibacterial therapy was performed according to clinical data (with persistent febrile neutropenia and local signs of inflammation) and the results of microbiological tests.

Antibiotic treatment was considered effective in registering normal body temperature and reducing clinical symptoms of inflammation.

Indications for surgery were considered to be the presence of abscesses, foci of necrosis and tissue destruction. The drainage of the abscesses, necrotomy were performed. In some cases (pelvic phlegmon), opening and drainage were combined with colostomy.

The statistical analysis was carried out using the database created for this study, and included the construction of feature distributions, verification of statistical homogeneity of samples (Wilcoxon rank criterion), frequency analysis, correlation analysis, and multivariate analysis (logistic regression).

Continuous data is presented as mean (with a span) or medians (with a span or 95% of coincidence interval), depending on the type of distribution, while categorical data is presented as frequencies and percentages.

RESULTS

Ninety-five episodes of PI were studied in 79 patients (44 females). The median age of patients was 35 years (ranging from 17 to 69 years). Most patients were diagnosed with acute leukemia – 43 (54.4%) and non-Hodgkin's lymphoma – 17(21.5%).

During the follow-up period, 67 (84.8%) patients had one PI episode, 12 (15.2%) patients had two or more PI episodes (Table 1).

PI episodes during GCP were statistically significantly more often than those without GCP: 74 (77.9%) vs 21 (22.1%), relative risk 3.5 (95% CI: 2.4-5.2), two-sided Fisher's exact test (Table2). A significant number of PI episodes developed in remission of the hematological disease in both patients with GCP (62.5%) and those without GCP (47.6%).

The greatest number of PI episodes on the background of GCP was observed during ChT (74.3%): more often at the stages of consolidation and induction of ChT of acute leukemia (28.4% and 13.3%, respectively) and ChT of lymphoma 20.3%. The PI episodes that occurred after BMT were also more often combined with GCP (allo-BMT 9.5% vs. 0, auto-BMT 6.8% vs. 4.8%; p=0.01). The PI episodes occurring without GCP predominated in the onset of hematological disease before the start of ChT (28.6% vs. 4.1%) and after the end of ChT (19.0% vs. 5.4%).

Patients with GCP were characterized by a combination of PI with other infectious complications (43.2%, versus 19% in patients without GCP, p=0.05). In the group with GCP, blood infections during PI were registered in 15 (20.3%) patients, 2 of them developed septic shock. Blood infections were not detected in the group without GCP.

In patients with severe GCP, local signs of inflammation in perianal tissues were clinically detected in 66 (89.2%) of 74 patients. The most often manifestation of PI in patients with GCP was inflammatory mass (71.6%). Necrosis/ulcers of the perianal tissues were observed in 7(9.5%) cases, and abscess formation in 6(8.1%). In 8 (10.8%) PI episodes, only perianal pain and fever were recorded, without inflammatory changes in soft tissues. According to MRI data, these patients showed signs of edema of perianal tissues (Fig.1).

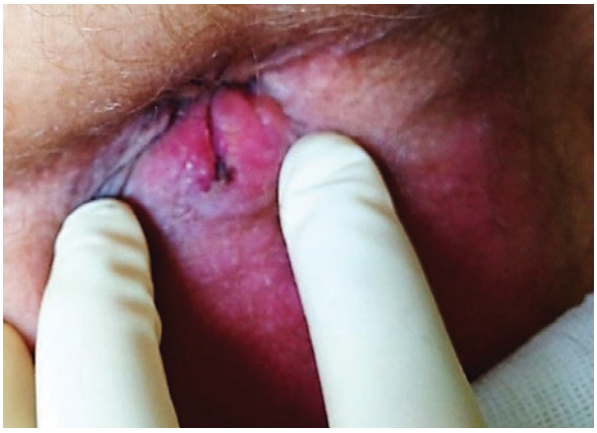

Figure 3. *Granulocytopenia. Anal fissure is the source of infection*

In patients without GCP, changes in the tissues were present in all observations. Abscesses predominated in this group (66.7)%.

When comparing the number of granulocytes in patients with various forms of PI, it was noted that the highest level of white blood cells was detected in patients with abscesses (both in patients with GCP and without GCP). The lowest number of white blood cells (median 0.2 (0.1-0.5)x10^9/l) was observed in patients with PI who had no visible changes in the perianal tissues (Fig.2).

Significant differences between the groups concerned the sources of infection of the perianal tissue. The classic pathogenesis of perianal abscess was typical for PI episodes without GCP: the most common source of infection was anal crypts (33.3% vs. 4.1%; p<0.001), fistulas (33.3% vs. 13.5%; p<0.001) (Table 2).

In patients with GCP, in most cases, inflammation was formed around defects in the walls of the anal canal or perianal skin: infection of anal fissures was more often noted (Fig.3) (66.2% vs. 19.1%; p<0.001), and ulcers of the perianal skin - 13.5%. In two cases, the sources of infection were postoperative wounds. Cryptogenic perianal infection made up only 4.1% of PI episodes with GCPs.

Table 3 shows the spectrum of microorganisms isolated at the time of PI development from the rectum and from the blood. A total of 111 microorganisms were isolated, among which enterobacteria prevailed (64%) due to *Escherichia coli* and *Klebsiella spp*. In 5 (4.5%) cases, *Pseudomonas aeruginosa* was detected on the anal mucosa.

Colonization of the intestinal mucosa by enterobacteria with the production of extended-spectrum β-lactamases (ESBL) was 40.5%, and vancomycin-resistant strains of *Enterococcus faecium* - 13.5%.

Bacteremia was detected in 15 PI episodes, in all cases against the background of GCP. In 6 observations, the species correspondence of microorganisms isolated from the rectum and blood was noted. Thus, PI was a microbiologically proven source of sepsis in 6(8.1%) of 74 patients.

Antibacterial therapy was the main method of treatment of PI in the study and was used in 88 (92.6%) of 95 EPI (Table 4). Only antibacterial therapy as a treatment for PI was used mainly during the period of GCP (87.8% vs. 23.8%; p<0.05). In 21(22.1%) cases, the first stage of PI treatment was urgent surgery.

Table 3. *Diversity of microorganisms in blood and in rectum detected via PI diagnostics*

Microorganisms	Selection locus		Coincidence of microorganisms isolated from the rectum and blood n=6
	Microorganisms in rectum n=111	Microorganisms in blood n=15	
Gramnegative bacteria	76(68.5)	12(75.0)	0
Enterobacteria ceae	71(64)	8(50.0)	0
Escherichia coli	47(42.3)	5(31.3)	2
Of them with the production of ESBL	26(23.4)	2(12.5)	1
Klebsiella spp	15(13.5)	3(18.7)	0
Of them with the production of ESBL	14(12.6)	2(12.5)	2
Other Enterobacteria	9(8.1)	0	0
Of them with the production of ESBL	5(4.5)	0	0
Total with the production of ESBL	45(40.5)	4(25.0)	3
Non-fermenting bacteria			
Pseudomonas aeruginosa	5(4.5)	4(25)	1
Grampositive bacteria	18(16.2)	3(18.8)	
Enterococcus spp	18(16.2)	3(18.8)	1
Enterococcus faecium vancomycin-resistant	15(13.5)	0	0
Candida			
Candida spp	17(15.3)	0	0

Table 4. *Variants of PI treatment*

Variants of PI treatment	Number of PI episodes, n (%)			p
	Total n=95	With GCP n=74	Without GCP n=21	
Antibacterial therapy	70(73.7)	65(87.8)	5(7.2)	<0.001
Combination of surgery and antibacterial therapy	18(19.9)	8(10,8)	10(47.6)	0.001
Only surgeries	3(3.2)	0	3	0.01
Surgery types				
opening the abscess	19(20.0)	6(8.1)	13(61.9)	
opening the phlegmon of the pelvis, a colostomy	1(1.1)	1(1.4)	0(0)	<0.001
excision of the fistula	1(1.1)	1(1.4)	0(0)	
Total operated on	21(22.1)	8(10.8)	13(61.,9)	<0.001
Onlylocal treatment was performed	4(4.2)	1(1.4)	3(14.3)	0.03

Table 5. *Antibiotic treatment outcomes in patients with PI*

Indicator	Number of PI episodes, n (%)		p
	With GCP n=74	Without GCP n=21	
Administration of starting antibacterial therapy:	73	15	
cefoperazone / sulbactam	44(60.3)	5(33.3)	0.01
carbapenems	20(27.4)	0	
Other antibiotics*	9(12.3)	10(66.7)	
Replacing start-up antibiotics with carbapenems	17(23)	2(13.3)	0.15
Use of carbapenems	37(50.7)	2(13.3)	0.01
Effectiveness of cefoperazone / sulbactam:			
in monotherapy mode	7(16)	3(60)	0.01
in combination with amikacin	13(29.5)	1(20)	
in combination with other medications**	7(16)	1(20)	
Effectiveness of carbapenems:			
in monotherapy mode	8(21.6)	1(50)	0.001
in combination with amikacin	9(24.3)	0 (0)	
in combination with other medications**	15(40.5)	1(50)	
Effectiveness of other antibiotics*	2(22.2)	8(80)	0.001
Overall effectiveness of antibacterial therapy	61(83.6)	15(100)	0.37
Average (range) duration of antibacterial therapy, days	16,1(3-67)	13,1(1-27)	0.19

**ciprofloxacin, mixofloxacin and amoxiclav, **vancomycin, linezolid and tygacil*

The majority of patients were operated on outside of GCP (61.9% vs. 10.8%, p <0.05). Cases of spontaneous regression of inflammation (1 in the group with GCP and 3 without GCP) were associated with the restoration of the number of white blood cells and local use of antiseptics.

Table 5 shows an analysis of the antibacterial therapy of PI. For the treatment of PI, antibiotics were more often prescribed during the period of GCP (98.6% vs. 71.4%). In patients with GCP, cefoperazone/sulbactam (60.3% vs. 33.3%) and carbapenems (27.4% vs. 0%) were used as the starting antimicrobial therapy significantly (p=0.05) more often. The drugs were administered only parenterally. It should be noted that in this group in 19(25.7%) of 74 episodes, the development of PI occurred against the background of antibacterial therapy for other infectious complications, and in two cases septic shock developed. For this reason, carbapenems were often the starting therapy for PI.

In the group of patients without GCP, antibacterial therapy was more often complementary to surgery. Starting antibacterial therapy in most episodes (66.7%) was performed with such drugs as ciprofloxacin, mixofloxacin, amoxiclav, which were prescribed both orally and parenterally.

These drugs were quite effective only in the group without GCP (80% vs. 22.2%, p=0.05).

When PI was combined with GCP, the effectiveness of antibiotic monotherapy was significantly lower (p=0.05) than in the group without GCP for both cefoperazone/sulbactam (16% vs. 60 %) and carbapenems (21.6% vs. 50 %).

The addition of other antimicrobial drugs to first-line antibiotics was used in 48 (55.2%) cases, more often in

Table 6. *Conservative and surgical treatment outcomes in patients with PI*

Indicator	With GCP, n (%)		Without GCP, n (%)		p
	Operated on	Conservative lytreated	Operated on	Conservative lytreated	
Number of PI episodes	8	66	13	8	
Administration of antibiotics	8(100)	65(98.5)	10(76.9)	5(62.5)	<0.001
Regression of inflammatory symptoms	7(87.5)	54(83.1)	13(100)	7(87,.5)	<0.001
The formation of an abscess/fistula	0(0)	9(13.8)	0 (0)	1 (12.5)	0.27
Progression of PI	1(12.5)	2(3.1)	0 (0)	0 (0)	0.19
Average (span) duration of an infectious episode, days	25,5(5-54)	15,1(1-67)	11,2(1-21)	15,2(3-27)	0.01

** frequency distributions are compared in the presence and absence of GCP*

Table 7. *Outcomes of PI treatment according to GCP duration*

Indicator	GCP duration, days		
	1-14	15-30	>30
Number of PI episodes	24	25	24
Administration of antibacterial therapy, n	23	25	25
A/b therapy modification, n (%)	4(16.7)*	6(24)	10(40)*
Administration of carbapenems, n (%)	9(37.5)	12(48)	13(52)
PI progression, n (%)	0(0)	0(0)	2(8)
Combination of PI with other infections, n (%)	6(25) **	15(60)	13(52) **
Bacteremia, n (%)	3(12.5) ***	5(20)	7(28) ***
Average duration of antibacterial therapy, days	8.3#	12.9	23.1#

, **, *, # – the difference is statistically significant (p<0.05)*

patients with GCP (69.9% vs. 20%). Amikacin was used more often - 58.3%; vancomycin - 19.4%; antimycotics - 27.8%.

In the group of patients with GCP, when amikacin was added, treatment was more often successful when cefoperazone/sulbactam was prescribed (17.8% vs. 9.6%). The addition of vancomycin (or linezolid) increased the cure rate for carbapenems (20.5% vs. 11%, p=0.05).

The carbapenem use at all stages of therapy was higher when PI was combined with GCP (50.7% vs. 13.3%; p=0.05).

To evaluate the results of treatment, an analysis of subgroups of operated and non-operated patients was performed (Table 6).

Antibiotic therapy of PI during GCP resulted in regression of signs of inflammation in tissues in 83.1% of cases; in 13.8% of cases, abscesses or fistulas that required surgery appeared during neutrophil recovery.

Among the operated patients with GCP, the regression of inflammatory symptoms was achieved in 87.5% of cases. It should be noted that in the group of patients with GCP, all operations were combined with antibacterial therapy. On average, the duration of antibacterial therapy was significantly longer in the group of operated patients with GCP than in the group treated conservatively (on average, 25 days versus 15, p=0.05).

When analyzing the factors that affect the recovery rate and the duration of therapy, the duration of the GCP period was of great importance (Table 7).

With an increase in the period of GCP to over 30 days, the rate of combination of PI with other infectious complications significantly increases from 25% to 60% (p<0.05). At the same time, PI is significantly more often accompanied by bacteremia (GCP up to 30 days - 12.5%, with GCP over 30 days - 28%; p<0.05), the need for modification of antibiotic therapy (16.7 vs. 40%; p<0.05) and the duration of antibiotic use (8.3 vs. 23.1 days; p<0.05).

No effect and progression of infection was observed in two patients with a duration of GCP of more than 30 days.

However, PI was not a direct cause of death in the study.

DISCUSSION

GCP has a decisive influence on the infectious complications rate in the Hematology unit. In 74(77.9%) of the 95 episodes in this study, PI developed during the period of GCP.

Similar data were demonstrated among patients examined in the NMRC of Hematology from 2009 to 2015 [12]. Most PI episodes during the period of GCP (74.3%) developed against the background of ChT courses.

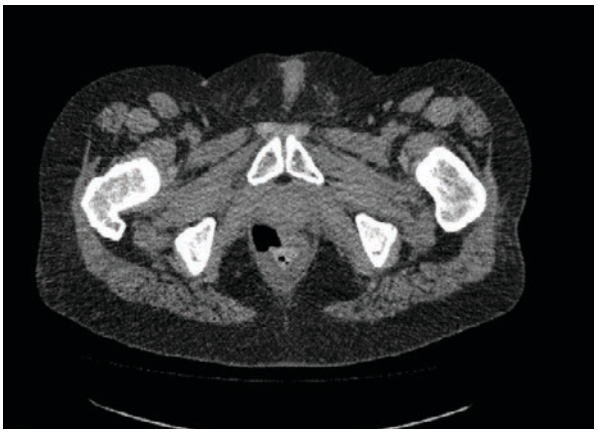

Figure 4. *Pelvic CT image. Patient L. Diagnosis: non-Hodgkin's lymphoma. Patient's status in the setting of high-dose chemotherapy, granulocytopenia. Rectum perforation, pararectal cavity containing gas*

The inflammation of perianal tissues formed on the background of GCP has peculiar features that differ significantly from perianal infection in immunocompetent patients [8,13].

The generally accepted explanation for the pathogenesis of perianal abscess, as well as perianal fistulas, is inflammation of the perianal tissue caused by the spread of the inflammatory process from the anal crypts and anal glands [13-15].

In the study, the absolute number of cryptogenic perianal infections was equal in both groups (13 vs. 14).

However, in patients with GCP, classical cryptogenic perianal abscesses (4.1%) and exacerbations of perianal fistulas against the background of existing perianal fistulas (13.5%) represented only a small proportion of PI cases.

In most cases, the infectious process in the perianal tissue during the period of GCP was an inflammation that formed around defects in the anoderm and perianal skin (Fig.3).

The absence of neutrophils determines the possibility for the appearance of additional mechanisms of infection - the spread of bacterial flora into the tissues and blood, both from the intestinal mucosa, and through skin damage to the anal canal and perianal area [1,8,12].

Therefore, in conditions of neutropenia, anal fissures, ulcers, erosive proctitis, dermatitis, and other processes that violate the barrier function of the skin and mucosa become frequent sources of infection of the perianal tissues [1,5,12].

There is no classification of changes in perianal tissues associated with GCP in the literature. In most publications abscesses, infiltrative inflammation, necrotic and ulcerative lesions are distinguished. According to the study that included patients with severe neutropenia and leukemia, anal pain (86%) is the most common manifestation of PI; tissue changes in the form of hyperemia and cellulite are present in 42%, and pus collection is rare (13.5%) [3]. In this study, inflammation during the period of GCP in most cases was represented by inflammatory mass (71.8%) and tissue necrosis (10.8%). It should be noted that abscess formation is a rare but possible manifestation of PI in GCP [6]. In this study, 6 (8.1%) of 74 PI episodes showed the formation of cavities in the perianal tissue during the period of GCP. The contents of such cavities were pus, and in the presence of a defect in the intestinal wall – faeces or gas (Fig.4).

Along with the forms of PI presented above, in some patients with severe GCP, it is impossible to visualize clear signs of infection that would be present in an immunocompetent patient [8]. In our study, 10.8% of PI episodes in patients with GCP occurred with severe pain, but without the classic signs of inflammation. Changes in the tissues were detected only by MRI imaging. The study of the relationship between the number of white blood cells and clinical forms of PI showed that the absence of visible changes in the tissues was at the lowest number of white blood cells (median 0.2 (0.1-0.5) $x10^9$/l) (Fig.2).

Thus, in some cases, the use of only clinical evaluation can be misleading [4]. Accurate data on the nature of changes in tissues are important, as they are the basis for choosing treatment tactics. GCP does not exclude the presence of cavities that require rapid drainage. The priority method of additional examination is MRI [4,8,13,14]. The most common microorganisms cultured from the blood and rectum in PI are enterobacteria and enterococci [3,5,7,16]. The predominance of enterobacteria as pathogens distinguishes PI from other types of skin and soft tissue infections, which are caused by streptococci or staphylococci [5]. In this study, among the pathogens of PI isolated from the rectum, the predominance of enterobacteria 63.96% was noted due to the strains of *Escherichia coli* and *Klebsiella spp*.

In recent years, there has been a trend to increase the number of infectious complications caused by gram-negative polyresistant microorganisms [1,5].

In this study, colonization of the intestinal mucosa with resistant strains was detected in 54% of cases, of which enterobacteria with ESBL production accounted for 40.5% and vancomycin-resistant strains of *Enterococcus faecium* 13.5%.

It should be noted that patients with GCP are characterized by a combination of infections and septic nature of infectious complications. In this study, blood infections were reported only in patients with GCP. PI was a microbiologically proven source of sepsis in 8.1% of the cases.

An important feature of PI treatment is the need to take into account many factors that determine approach.

These factors include the form of inflammation, the presence or absence of indications for surgical treatment, the presence of GCP, its expected duration, the severity of the patient's condition, the presence of other infectious complications, and the therapy performed at the time of PI registration.

If the treatment of perianal acute abscess in immunocompetent patients is only surgical [13,14], then the presence of PI in patients with GCP is an indication for the urgent initiation of antibacterial therapy. The results of a number of studies confirm the possibility of successful treatment of PI in such patients with broad-spectrum antibiotics [2,5,10,16].

In the study, the need for antibacterial therapy in GCP was in all cases, both in the group of operated and non-operated patients.

Only antimicrobial therapy for GCP was performed in 87.8% of the cases, in combination with surgery - in 10.8%.

We follow an escalating approach to antimicrobial therapy, which involves prescribing cefoperazone/sulbactam or piperacillin/tazobactam, active against *Enterobacteriaceae* bacteria at the initial stage of infection [17]. Further modification of therapy is carried out according to the results of microbiological studies. The reason for the appointment of carbapenems as the starting therapy for PI (27.4% of cases) was the presence of sepsis, septic shock, and the development of PI against the background of already ongoing antibacterial therapy.

Thelow effectiveness of both β-lactam antibiotics and carbapenems in the monotherapy mode was a feature of the antibacterial therapy of PI in the conditions of neutropenia. The addition of other antimicrobials was required in 70.8% of cases.

Antibacterial therapy of PI in patients without GCP was successfully performed in the mode of monotherapy with β-lactam antibiotics, fluoroquinolones, and amoxiclav. Oral medication was also possible in this group of patients.

Among the factors that influence the prognosis of PI and the strategy of antibacterial therapy, the duration of the GCP period is of great importance [7,17,18].

In our study, with an increase in the duration of GCP from 1-14 to over 30 days were associated an increase in the bacteremia rate (12.5% vs. 28% $p<0.05$), a combination of PI with other infections, the need for modification of antibacterial therapy (16.7% vs. 40% $p<0.05$), and the duration of antibiotic use (8.3 vs. 23.1 days; $p<0.05$).

The need for surgery in patients with GCP occurs in the presence of cavities or foci of tissue destruction. In patients with GCP, antimicrobial therapy should be started simultaneously with surgery and continued in the postoperative period until the signs of infection completely disappear.

With this approach, there were no significant complications associated with surgery, including in patients with GCP [7,8]. However, surgery in the period of GCP is associated with an increase in the duration of the infectious episode and antibacterial therapy.

CONCLUSION

The GCP significantly increases the risk of PI. PI developed under the conditions of GCP is characterized by atypical, often poor clinical manifestations and a high risk of sepsis. Most PI episodes in patients with GCP are not associated with the classic cryptoglandular mechanism of perianal abscess formation. The main mechanism of infection of perianal tissue during GCP is the penetration of microorganisms through damaged tissue barriers. Antibacterial therapy is a priority method of treating PI in the conditions of GCP; the effectiveness of antibacterial therapy was 83.1%. The need for surgical treatment during GCP is associated with an increase in the duration of an infectious episode and antibacterial therapy. An increase in the GCP duration is an unfavorable predictor in the PI treatment.

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