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PERIANAL INFECTIONS AS A FIRST PRESENTATION OF HEMOBLASTOSIS AND APLASTIC ANEMIA

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AIM: to present clinical variability of perianal infection (PI), developed in the debut of oncohematological disease and to determine the factors that impede PI relief and time of antitumor treatment initiation, as well as the causes of complications during chemotherapy (ChT).
PATIENTS AND METHODS: the analysis included 8 patients with an infectious process in the perianal area developed in the debut of hemoblastosis and aplastic anemia (before ChT).
RESULTS: in 5 of 8 patients there was a long time between start of PI and the start of ChT for hemoblastosis (from 18 to 49 days). The impediment for a timely start of ChT was unspecified diagnosis of hemoblastosis (acute myeloid leukemia – 2 cases, multiple myeloma – 1, lymphoma – 1) and the ongoing infectious process in patients with severe granulocytopenia (GCP).
Usually undetected hematological malignancies were observed in patients with compensated data of haemogram. Complications during ChT were associated with recurrence of PI in the surgery area (palliative drainage of anorectal abscess and fistula-in-ano) and of the sepsis with persisted inflammation in the postoperative wound on the background of GCP.
CONCLUSION: PI is one of the infectious complications peculiar for the debut of oncohematological disease. Therefore, a general blood test with leukocyte formula should be performed before surgery in all patients with paraproctitis to exclude hemoblastosis. The unspecified diagnosis of hemoblastosis and the ineffectiveness of surgical treatment of paraproctitis in patients with severe GCP were the main reasons for the delay in the beginning of antitumor treatment in this study.
Persistent infection (fistula-in-ano) and the persistent inflammation in the wound on the background of the GCP has resulted in the recurrence of PI and sepsis during chemotherapy.

[Key words: perianal infection/ abscess, leukemia, hemoblastosis, neutropenia, granulocytopenia]

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AA – aplastic anemia
GCP – granulocytopenia
MM – multiple myeloma
ALL – acute lymphoblastic leukemia
AML – acute myeloid leukemia
PI – perianal infection
ChT – chemotherapy

Infectious complications are a frequent clinical form of hemoblastosis manifestation. The incidence of perianal infection (PI) is 5.8-7.9% among adult patients with acute leukemia [1,2], in 13.0-20.0% of these patients, perianal infection develops in the debut of hemoblastosis and serves as the first reason for seeking medical help [3,4]. Manifestations of perianal tissue infection in such patients are often atypical and can range from small perianal cellulitis to life-threatening sepsis [5,6].

The severity of developing hemoblastosis and immunodeficiency associated with bone marrow lesions and development of granulocytopenia (GCP) determine the patient's condition, course and prognosis of PI. Vital tasks are not only the relief of the infectious process, but also the early start of specific antitumor treatment. According to most authors, the parameters that determine surgical tactics in this pathology are the form of inflammation and the number of granulocytes. The formation of an abscess serves as an indication for urgent operative drainage [4,5,7,8]. In the group of patients with inflammatory infiltrates, treatment tactics should take into account the severity of GCP (which is, as a rule, the background for this type of inflammation), the high probability of sepsis and the lack of precise borders of inflammation in the tissues [3,7]. Frequent sources of infection of perirectal tissue in granulocytopenia are acute anoderm lesions and chronic diseases of the anal canal (fissures, ulcers, fistulas) [3,4]. Traditional surgical treatment in such patients is often associated with high mortality [1].

The results of treatment of patients with GCP and PI

are presented in a number of retrospective studies [1,8-10]. The authors note that in the group of operated patients mortality is the same or higher, compared with the group of patients treated conservatively (with antibiotics).

The possibility of intraoperative complications in patients with unrecognized leukemia is presented in the publication by Slater, D. N., 1984. The author described the death of a patient operated on for acute anorectal abscess from septic shock in the early postoperative period. Acute leukemia was diagnosed after surgery [11].

Understanding how hematologic disease changes the course of PI is essential for diagnosis and successful treatment. For this purpose, we analyzed the medical history of patients in whom the manifestation of oncohematological disease was inflammation in the perianal area.

AIM

To present clinical variants of perianal infection (PI), developed in the debut of oncohematological disease. To determine the factors that impede PI relief and time of antitumor treatment initiation, as well as the causes of complications during chemotherapy (ChT).

PATIENTS AND METHODS

The study included 8 patients who had symptoms of perianal infection developed as a hemoblastosis manifestation before treatment.

The patients were admitted to our Center, or were transferred from other hospitals, where they turned for the anorectal diseases. The clinical features of the patients were studied: the presence of severe GCP (severe GCP is (agranulocytosis), decrease in the absolute number of granulocytes – less than 0.5×10^9/l), forms of inflammation in the perianal area, sources of infection, the presence of other complications characteristic of hemoblastosis. Methods of treatment were divided into urgent surgeries (opening of abscesses, excision of infiltrates), elective procedures (fistulectomies) and conservative therapy (antibiotics).

Assessing the treatment modalities, we estimated their effectiveness in elimination of infection and the impact on the main disease treatment. We analyzed the period from the patient's request for medical care for PI to the beginning of pathogenetic treatment of the main disease, comparing it with the clinical features and chosen treatment. The morbidity associated with PI during chemotherapy and its possible causes were also assessed.

Statistical analysis of the data included standard descriptive methods and correlation analysis.

RESULTS

In the period from 2016 to 2018 perianal infection complications were detected in 98 patients with hemoblastosis at different stages of treatment. In 8 of them, signs of PI developed in the debut of hemoblastosis before the treatment: in 6 men and 2 women, aged 17-62 years. In 5 of them, the blood disease was detected and the PI treatment was carried out taking into account hemoblastosis. In the remaining 3 cases, at the time of the PI treatment the diagnosis was not established (two patients were subsequently diagnosed with acute myeloid leukemia (AML) and one patient with multiple myeloma (MM)). Manifestations of PI were different: exacerbation of chronic diseases (fissures, fistulas), formation of cryptogenic abscesses or exacerbation of anorectal chronic inflammation.

Inflammation developed both against the background of normal granulocyte number (in five patients) and against the background of severe GCP (agranulocytosis – in three patients) (Table 1). However, 1 patient developed an abscess under conditions of deep leukopenia (leukocytes 1.84×10^9/l).

Of the five patients without GCP, four were operated on urgently or elective before the start of ChT. Indications for surgery in this group were: formation of abscesses in 3 patients, exacerbation of inflammation in the area of fistula-in-ano in1 patient (Table2). One patient with advanced hemorrhagic syndrome underwent conservative antibacterial therapy for a fistula-in-ano. In all of them PI relief and cleansing of the postoperative wound were noted.

Infection of the postoperative wound or sepsis after the ChT course were not noted in any case, regardless of the start time.

In three patients during the PI development severe GCP was detected (the absolute number of granulocytes was less than 0.5×10^9/l) (Table 2). The PI manifestation in two cases was the development of inflammatory infiltration around a chronic fissure or fistula and in one – the abscess formation. One patient was treated with antibiotics and local antiseptics. This tactic allowed to stop inflammation, so the induction ChT course was not postponed. Inflammation in the post-course period did not increase, as it was controlled by antibacterial therapy. Two patients were operated on (opening of the abscess and the fissure excision). In the postoperative period, due to persistent inflammation in the postoperative wound area and hyperthermia, long-term antibacterial therapy was required (for 18 and 38 days).

Table 1. *Characteristics of patients*

Indications	Number of patients
Age range (average), years old	37 (17-62)
Gender (female/male)	2/6
Diagnosis: Acuteleukemia Multiple myeloma Non-Hodgkinlymphoma (NHL) Aplastic anemia (AA)	 5 1 1 1
Clinical forms of PI: Anorectal abscess or inflammatory mass Fistula-in-ano Anal fissure, anorectal inflammatory mass Exacerbation of anorectal chronic inflammatory mass, abscess	 3 3 1 1
The diagnosis of hemoblastosis at the time of PI treatment was established	5
Granulocytopenia (granulocytesless than 0.5×10^9/l)	3
Treatment of PI was carried out at NRC of Hematology Transferred from other hospitals	4 4

Table 2. *Treatment options for perianal infection in groups of patients with and without granulocytopenia*

Treatment options	Groups of patients		In total
	There is granulo-cytopenia (n=3)	No granulo-cytopenia (n=5)	
Urgentsurgeries	2	3	5
Indications:			
Cryptogenic anorectal abscess	1	2	
Exacerbation of anorectal chronic inflammatory mass, abscess		1	
Anal fissure, anorectal inflammatory mass	1		
Elective procedures		1	1
Indications:			
Fistula-in-ano		1	
Antimicrobial therapy only	1	1	2
Indications:			
Fistula-in-ano	1	1	

In 5 (out of 8) patients, there was a significant increase in the time between seeking medical care for PI and the ChT initiation for hemoblastosis (from 18 to 49 days) (Fig. 1). Aggressive hemoblastoses (AML, ALL, NHL) requiring immediate ChT start were in 6 out of 8 patients.

In the group of the patients without GCP, the ChT was started in the terms of 3 to 49 days. The delayed start (in 3 patients) was due to the fact that the diagnosis of hemoblastosis was not timely established (acute myeloid leukemia – 1, multiple myeloma – 1) or required clarification and additional examination (non-Hodgkin's lymphoma-1). The diagnosis was established during repeated visits against the background of the state deterioration and other complications (Table 3). In the group of the patients with GCP, diagnosis of hematologic disease was performed before the beginning of PI treatment or in the early postoperative period.

The reason for postponing ChT start in two cases (18 and 38 days) was persistent inflammation in the postoperative wound and hyperthermia in operated patients (Table 3).

In 5 patients with perianal infection, complications characteristic of hemoblastosisprogression were noted: hemorrhagic syndrome (2 patients with AML), renal failure requiring hemodialysis (1 patient with multiple myeloma), other foci of infection (2 patients with AML and AA), severe anemia and dependence on transfusions (the patient with AA).

Concomitant complications were specific to a particular hematologic disease.

Perianal inflammatory complications during ChT were noted in 2 cases. In the group of patients without GCP, a recurrence of anorectal abscess was noted. The cause of relapse was a preserved internal opening of the fistula in the anal canal after abscess drainage. In another case, immunosuppressive therapy with ongoing inflammation in the postoperative wound on the background of GCP was complicated by the spread of infection and the sepsis development (Table 4).

Clinical case

Female G., 48 years old.

It is known that in early March 2018, the patient had complaints about weakness and febrile fever. Two weeks later, pain in the anal canal joined. The patient suffered from chronic anal fissure, independently carried out local conservative treatment with effect.

The «aggravation of the anal fissure» was the first reason for going to the doctor. The patient was admitted to the Proctology Department of one of the municipal clinical hospitals with a diagnosis of «Chronic anal fissure. Anorectal infiltrative inflammatory mass» and was urgently operated on (on 22.03.2018). The fissure excision was performed.

Simultaneously, the first tests were performed. The blood tests revealed three-growth cytopenia, deep leukopenia and blastemia. (The general blood test of

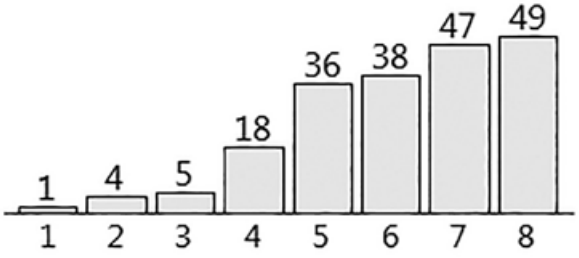

Figure 1. *Periods from admission of patients to the hospital for medical care about perianal infection and before the treatment of hemoblastosis (on the x-axis: patients)*

22.03.2018 is as follows: hemoglobin 95 g / l, thrombocytopenia 118×10^9/l, leukopenia 1.8×10^9/l, 14% blast cells).

In the postoperative period pain, inflammation in the perianal area and fever persisted: so antimicrobial therapy was carried out according to various schemes. To clarify the diagnosis and treatment modalities, on 29.03.2019 the patient was hospitalized.

At admission, the patient's condition was poor, due to the main disease, infectious complications: focal pneumonia, perineal infection, post injection thrombophlebitis of the veins of the right forearm. In the laboratory data (of 30.03.2018): increase of anemia and thrombocytopenia (hemoglobin 82 g/l; erythrocytes 2.39×10^{12}/l; platelets 78×10^9/l); tumor agranulocytosis (leukocytes 0.86×10^9/l; neutrophils 0.01×10^9/l).

When examined on the basis of bone marrow punctuate and trepan biopsy (blastosis in the bone marrow – 74.8%, cytochemically blast cells of myeloid orientation were detected), the diagnosis was made: Acute myeloblastic leukemia.

Upon admission to the Center, the patient had complaints about moderate pain and bleeding in the anorectal area. When examined on the back wall of the anal canal, the postoperative wound of 2×3 cm was determined, the adjacent tissues were moderately hyperemic, edematous. Signs of inflammation were determined on the perianal skin and on the opposite wall of the anal canal (Fig. 2). Taking into account the continuing inflammatory process in the perianal area, antibacterial therapy was continued (Cefoperazone/sulbactam 4.0×2 times/day i/v, amikacin 0.5×2 times/day i/v).

Against the background of antibacterial therapy, the subfebrile temperature remained with a short-term increase to 38.2 °C without chills in the evening.

Given the progressive nature of the main disease, an unfavorable prognosis, it was decided to conduct an induction course of chemotherapy. From 06.04.18 to 20.04.18 the ChT induction course was conducted under the «Asa-IdaAra-C» program. After introduction of cytostatics, a further deepening of leukopenia was noted: the total number of leukocytes decreased to 0.4×10^9/l.

Since 12.04.2018, there has been an increase in pain in the perianal area.

Against the background of myelotoxic agranulocytosis, acute infiltrative anorectal mass developed: a subcutaneous inflammatory infiltrate of 3×3 cm appeared around the postoperative wound on the back wall of the anal canal, the bottom of the wound was covered with fibrin.

On 23.04.2018 the patient's state deteriorated sharply. The temperature rose to 39 °C, hemodynamic instability, tendency to hypotension, positive markers of bacterial sepsis (procalcitonin test was over 10 ng/ml) were noted.

During the entire period of hospitalization, microflora

Table 3. *Period of treatment (about perianal infection) and the start of chemotherapy and the reasons for delayed initiation of chemotherapy*

Parameter	Groups of patients	
	There is granulocytopenia (n=3)	No granulocytopenia (n=5)
The period from seeking medical care (for PI) to the beginning of ChT, days (average, range)	20 (4-38)	28 (3-48)
Causes of delayed start of ChT: the absence of a diagnosis of hemoblastosis, ongoing PI	 1 2	 3

Table 4. *Characteristics of complications in groups of patients with and without granulocytopenia*

Types of complications	Groups of patients	
	There is granulocytopenia (n=3)	No granulocytopenia (n=5)
Complications associated with the progression of hemoblastosis: Infectious complications Hemorrhagic syndrome Renal failure Severe anemia, need for blood transfusions	 2 1	 1 1
Perianal inflammatory complications developed in the period of PChTs: PI relapse Sepsis	 1 1	 1

Figure 2. *Postoperative wound and other sites of infections in the perianal region*

Table 5. *The results of bacteriological tests of patient G*

Bacteriologicaltests	The results of the study on 03.04.2018, 17.04.2018	The result of the study on 24.04.2018
Microbiological tests of a smear from the intestinal mucosa	*Escherichia coli* without BLRS production*, moderate growth	*Escherichia coli* BLRS, sensitive to carbapenems, abundant growth
Microbiological (cultural) blood test for sterility	No growth	A positive blood culture *Escherichia coli* BLRS sensitive to amikacin and meropenem
Antibacterial therapy	For29.03.-22.04.18 with cefoperazone/ sulbactam + amikacin	For 23.04.18-03.05.18 with meronem +amikacin

** Extended – spectrum BLRS-β-lactamases*

from the anal canal and blood were monitored (Table5). On 24.04.2019 positive hemoculture of Escherichia coli with the extended-spectrum BLRS-β-lactamases production was isolated.

A similar microorganism was obtained from the anal canal. Taking into account the clinical picture and species correspondence of microorganisms isolated from the postoperative wound and blood, it was established that the postoperative wound was a source of sepsis.

Antibacterial therapy was escalated: cefoperazone / sulbactam was replaced with meronem. The effect of antibacterial therapy in the form of reducing temperature to subfebrile values was obtained on the 2nd day. Antibacterial therapy was continued for 10 days until the increase in the number of leukocytes and inflammation regression (on 03.05.2018). Recovery of hematopoiesis was noted on the 25th day after the course. Blastosis in the myelogram decreased to 1%, which allowed us to talk about remission of the main disease. Against the background of normalization of blood parameters, the signs of inflammation in the perianal area regressed, the wound cleared. Further implementation of the ChT program took place without signs of perianal complications.

DISCUSSION

Forms of inflammation developing in anorectal zone at the debut of hemoblastosis are different: anorectal abscesses, inflammatory mass, fistulas. The number of granulocytes largely determines heterogeneity of clinical forms of inflammation.

Formation of abscesses was observed in patients with preserved granulocyte number, whereas in their absence inflammatory infiltrates (perianal cellulitis) are characteristic, often associated with anal fissures and fistulas.

Most patients in this study (6 out of 8) were operated on. The effectiveness of surgical procedure also depended on the safety of granulocytes.

The presence of granulocytes provides purification of wounds, formation of a granulation barrier that blocks the spread of infection beyond the wound. Therefore, the course of the wound process in the group of patients without GCP was favorable, and immunosuppression was possible in the presence of a clean postoperative wound.

In conditions of severe GCP this mechanism is lost, wounds can serve as a source of inflammation and sepsis even after a long time after surgery.

The inflammatory process that persisted after the surgery required long-term and massive antibacterial therapy and was an obstacle to the beginning of pathogenetic treatment.

Early diagnosis and urgent initiation of antimicrobial therapy is the preferred tactic in the conditions of GCP. With the use of this approach many authors associate significant reduction in mortality in patients with PI and GCP in recent years. So, Lehrnbecher [8] in a study conducted at the National Cancer Institute, USA, showed a reduction in mortality from PI for over 10 years from 15.9% to 0%. The scheme of antibacterial therapy should include drugs with activity against gram-negative and anaerobic bacteria, take into account frequent presence of resistance to anti-

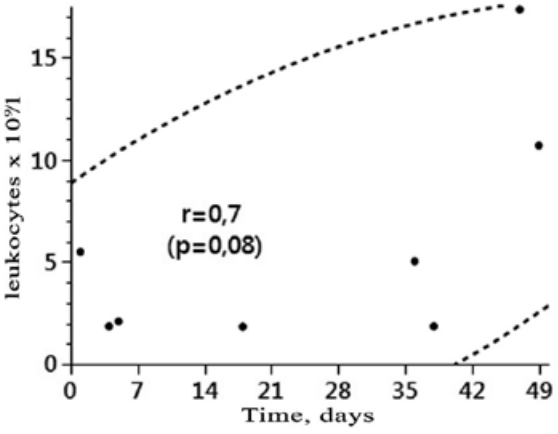

Figure 3. *The relationship between the time interval between patients' (n=5) admission to the hospital for medical care about perianal infection and the start of treatment for hemoblastosis (x-axis) and their leukocyte level (10^9/Liter) (y-axis): there is (close to statistical significance) positive correlation (Spearman's correlation coefficient: 0.75). It is valid only for patients without detected granulocytopenia (agranulocytosis)*

microbial drugs [12-13].
The main reasons for the late start of ChT (Fig. 1) were undiagnosed hemoblastosis (3 patients: AML – in 2 and MM – in 1) and ongoing infection in the perianal area (2 patients with GCP).
Hemoblastosis remained «unrevealed» in patients (3 out of 8) with compensated hemogram indices (Fig. 3), which may be due to the «typical» course of inflammation, the absence at the time of treatment of other complications.
In patients with severe GCP, the diagnosis of hemoblastosis was established quickly enough, however, the beginning of pathogenetic treatment (due to the ongoing infectious process) was also delayed (by 18-36 days).
Late diagnosis and delay in the beginning of antitumor treatment lead to development of other complications peculiar to hemoblastosis progression. In this case series in half of the patients, the appearance of other foci of infection and the occurrence of such severe complications as hemorrhagic syndrome, severe anemia, renal failure were noted.
Perianal inflammatory complications during ChT were associated with infection recurrence in the surgical area and the sepsis development. The cause of complications were persistent sources of infection: in one case – ongoing inflammation in the wound on the background of GCP; in the other – palliative drainage of abscess and a preserved internal opening of anorectal fistula.
Thus, given the severity of immunodeficiency, treatment of PI in oncohematological patients should include early adequate antibacterial therapy.
Surgery is indicated in the presence of cavities and, given the upcoming ChT, should include elimination of a potential source of infection recurrence.

CONCLUSION

PI is one of the infectious complications characteristic of the debut of oncohematological disease. Therefore, a general blood test with leukocyte formula should be performed before surgery in all patients with anorectal infection to exclude hemoblastosis.
Undiagnosed hemoblastosis and ineffectiveness of surgical treatment of anorectal infection in severe GCP were the main reasons for the delay in the beginning of antitumor treatment in this study.
Persistent sources of infection (fistula) in the anal canal and continued inflammation in the wound on the background of GCP were the causes of PI relapses and sepsis during chemotherapy.

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