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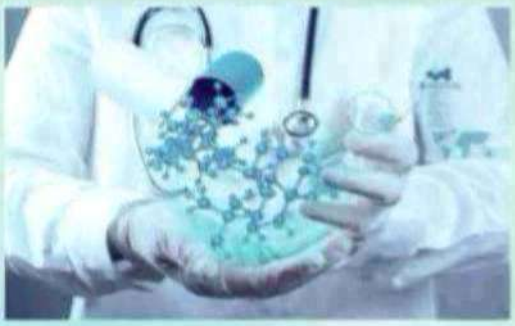

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CLINICAL AND PATHOGENETIC RELATIONSHIP BETWEEN IMMUNOLOGICAL CHANGES IN THE PERIOPERATIVE PERIOD IN CANCER PATIENTS

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✓ ***Resume***

As a result of the complex analysis, a systemic interdependence was established between the nature of the perioperative immune response, the type of anesthesia and the probability of the formation of an immunosuppressive state. The data obtained allow us to build a substantiated pathogenetic model in which the anesthetic effect acts not as a neutral component of pain relief, but as an active modifier of the immune balance in the conditions of an oncological disease

Keywords: oncology, surgery, anesthesia, immunity

ХАРАКТЕР ИММУНОЛОГИЧЕСКИХ ИЗМЕНЕНИЙ В ПЕРИОПЕРАЦИОННОМ ПЕРИОДЕ У ОНКОЛОГИЧЕСКИХ БОЛЬНЫХ

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✓ ***Резюме***

В результате комплексного анализа установлена системная взаимозависимость между характером периоперационного иммунного ответа, видом анестезии и вероятностью формирования иммуносупрессивного состояния. Полученные данные позволяют выстроить обоснованную патогенетическую модель, в которой анестезиологическое воздействие выступает не как нейтральный компонент обезболивания, а как активный модификатор иммунного баланса в условиях онкологического заболевания

Ключевые слова: онкология, операция, анестезия, иммунитет

OPERATSIYADAN OLDINGI DAVRDAGI ONKOLOGIK BEMORLARNING IMMUNOLOGIK O‘ZGARISHLARNING XUSUSIYATLARI

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✓ ***Rezyume***

Kompleks tahlil natijasida perioperativ immun javobning tabiati, og‘riqsizlantirish turi va immunosupressiv holatni shakllantirish ehtimoli o'rtasida tizimli o'zaro bog'liqlik aniqlandi. Olingan ma'lumotlar bizga asosli patogenetik modelni yaratishga imkon beradi, unda anestetik ta'sir og'riqni yo'qotishning neytral komponenti sifatida emas, balki onkologik kasallik sharoitida immunitet muvozanatining faol modifikatori sifatida namoyon bo‘ladi

Kalit so'zlar: onkologiya, jarrohlik, anesteziya, immunitet

Relevance

The problem of perioperative immunosuppression in cancer patients has been actively discussed in the scientific literature since the end of the 20th century, when it became obvious that surgical intervention, despite the radicality of tumor removal, is often accompanied by an increased risk of metastasis. Works of this period established that the tissue trauma itself, accompanying the operation, causes activation of the neuroendocrine stress axis and subsequent systemic immunosuppression (1,3,5).

The first observations of the relationship between anesthesia methods and changes in immune status date back to the 1990-2000s. It was shown that the use of inhalation anesthetics is associated with a more pronounced decrease in the activity of natural killers and an increase in the level of proinflammatory cytokines than total intravenous anesthesia. This marked the beginning of the search for optimal anesthetic approaches for cancer patients (1,2,4,6).

The data accumulated to date have allowed us to put forward a hypothesis about the need for a comprehensive assessment of the immune status of patients in the perioperative period. In the studies of some authors, attempts were made to stratify patients by immune profile and select individualized anesthetic tactics to minimize immunosuppression (5,7,8,9). Thus, the degree of study of the problem indicates recognition of the high significance of perioperative immunosuppression as one of the key factors of unfavorable prognosis in cancer patients. However, the issues of individualization of anesthetic tactics, development of standards of immune correction and determination of reliable biomarkers of relapse risk remain unresolved, which determines the need for further targeted studies.

The aim of the study: to identify clinical and pathogenetic relationships between registered immunological changes and the development of adverse clinical outcomes in cancer patients who underwent surgery under conditions of different anesthetic support**.**

Materials and methods

The analysis was conducted based on observations of 60 patients without interference in the immune status, and was aimed at determining those immunological parameters that are associated with impaired early postoperative recovery, the development of complications or signs of a systemic inflammatory response. For subsequent analysis, threshold values of immunological indicators were determined that reflect the severity of cellular and humoral shifts, which we used for an objective quantitative assessment of immunosuppression in the context of clinical manifestations and the choice of an anesthetic approach**.**

The patient's hemodynamic response to surgery is one of the most sensitive and clinically understandable indicators of physiological stress. At the same time, it is a powerful provoking factor for the immune system, which should not just react, but adapt without losing its selective activity. We assumed that it is the depth and nature of hemodynamic fluctuations that can be reflected in the immunological profile, and decided to look at these conditions not as a score scale, but as a physiological scenario in which the immune system plays the role of a hidden protagonist. In patients who underwent surgery without any hemodynamic deviations, the immune picture remained surprisingly smooth. In almost all subgroups (be it general, regional or combined anesthesia), the CD4+ level fluctuated within the normal range (from 38 to 39%), NK cells were maintained in the "working range" (14-15%), and IL-6 did not exceed the physiologically acceptable threshold. These figures speak for themselves: under conditions of stable hemodynamics and controlled surgical stress, the immune system does not panic, but on the contrary, mobilizes rationally. The situation changes when transient pressure fluctuations occur that do not require intensive support. In this quasi-critical zone (when the body is not threatened by decompensation, but the stress axes are already turned on), the first pre-signals appear. In the general anesthesia subgroup, the CD4+ level dropped to 34.7%, which is already on the verge of the functional threshold, IL-6 rose above 40, and NK cells were below 13%. These values cannot yet be called critical, but they give reason to assume that if the situation worsens, the system may not withstand it.

And finally, where vasopressors were no longer needed, real immunosuppression developed. This was especially evident in patients with general anesthesia: CD4+ fell to 29.6%, NK - to 9.2%, IL-6 exceeded 50, and Treg rose to 7.5%, that is, crossed the border of regulatory hyperactivity. In this combination (reduced antitumor control and increased inhibitory regulation), the very model that we will further define as an immunosuppressive profile begins to emerge. What is noteworthy is that with regional anesthesia, even in the case of unstable hemodynamics, the indicators remained within moderate limits: CD4+ remained at 34-35%, NK - at 11-12%, and Treg did not demonstrate systemic growth. The combined approach showed similar, perhaps even slightly more restrained dynamics, which again confirms its immunological potential.

Thus, it can be stated: the depth of hemodynamic destabilization correlates with the severity of immune disorders, and this relationship is enhanced under general anesthesia. Immunosuppression here is not only a biological effect of anesthesia, but also a reflection of the complexity of adaptation mechanisms under conditions of general physiological stress.

Pain is perhaps the most ancient and at the same time the most subjective signal of the body. How a patient tolerates pain syndrome after an oncological operation depends on many factors (from the localization of the intervention to the psychological background). But behind all these external circumstances lies one indisputable fact: pain stress is a trigger for an immune response, and its nature can be no less important than the intensity of the pain sensation itself.

In this part of the analysis, we compared the immunological status of patients depending on how intense the need for analgesia was in the first day after surgery. Let's start with a favorable scenario, when the basic analgesia regimen was sufficient. In such patients, regardless of the type of anesthesia, a calm immune picture was observed. The CD4+ level remained within 38-39%, NK cells remained above 14%, IL-6 did not exceed 30 pg/ml, and Treg remained at a physiological level of about 5%. Such a profile could be called adaptive: the body encountered pain, but did not perceive it as a threat, and remained in a state of moderate tension, not panic. However, as the pain syndrome increased, especially when additional analgesics were required, the immune response began to shift. This was especially evident in patients who received general anesthesia. Here, CD4+ decreased to 33.9%, NK cells dropped to 11.9%, IL-6 rose above 40, and Treg - to 5.9%. This is not yet a critical level, but it is already a risk zone: signs of a breakdown of the cellular link appear first. In patients on regional and combined anesthesia, such shifts were also recorded, but they were less pronounced and did not go beyond the permissible fluctuations. But the real differences became obvious in patients experiencing severe pain syndrome requiring intensive opioid cover. In the OA group, an almost mirror image of immunosuppression was observed: CD4+ decreased to 29.2% - below the physiological threshold, NK - to 9%, IL-6 exceeded 54 pg / ml, and Treg rose to 7.6%. This is no longer just a “reaction” to pain, it is an immune capitulation, especially considering that these same patients more often had hemodynamic instability, high temperature, and signs of an inflammatory response. Opioids are known to be able not only to alleviate suffering, but also to interfere with the immune system by modulating μ-receptors, regulating T-cell activity and proinflammatory mediators. And in this situation, it was apparently the combination of severe pain and general anesthesia that created the worst immune scenario.

Against this background, the contrasting results of the RA and OA+RA subgroups look especially indicative. Even in patients with severe pain syndrome, but with a regional component, the immune system retained its basic reactivity. CD4+ decreased, but not dramatically. NK cells remained at a level of ≥12%, and IL-6 rose to moderate values. This may be due to the fact that regional anesthesia blocks the conduction of pain impulses at the peripheral level and reduces the activation of stress axes, thereby “protecting” the immune system from excessive excitation.

Thus, the analysis of this position of the scale allows us to make an important pathogenetic conclusion: the intensity of the pain syndrome and the method of its relief are directly related to the severity of postoperative immunosuppression, and the greatest damage is observed with a combination of severe pain, opioid load and general anesthesia. In patients whose awakening was rapid and calm, without signs of disorientation or vegetative instability, the immune profile indices remained almost identical to the norm. CD4+ was maintained in the range of 38-39%, NK cells - about 14.5%, IL-6 did not exceed 30 pg/ml, and the level of regulatory T cells remained within 5%. Regardless of the type of anesthesia used (general, regional or combined), this group demonstrated a physiologically favorable pattern, which can be considered a marker of normal immune awakening.

However, the situation began to change with a prolonged but formally uncomplicated awakening. These were the patients who woke up slowly, with mild inhibition, were not always confident in orientation in space, but without pronounced cognitive disorders. They already had a moderate decrease in CD4+ - especially in the OA subgroup (up to 34.2%), an increase in IL-6 to 39-40 pg/ml, and a decrease in NK cells to 12-13%. Such data indicate that even without visible clinical symptoms, at the level of neuroimmune interaction, the body assesses the situation as potentially threatening. The most important group of patients turned out to be those with delayed awakening, confusion, psychomotor agitation, that is, those who are described in the clinic as "difficult to exit". Here, a striking contrast was revealed. In patients with general anesthesia, the CD4+ level dropped to 28.7%, NK cells to 8.8%, IL-6 rose above 50, and Treg exceeded 7.7%. That is, against the background of neurovegetative destabilization, massive immune destruction was also triggered. Moreover, these patients often needed drug sedation after awakening, which in turn further prolonged the immunosuppressive window.

Results and discussions

Regional and combined anesthesia in this context showed a more restrained profile. Even with difficult awakening, the indicators decreased, but not so aggressively. CD4+ remained around 33-34%, NK did not fall below 11%, IL-6 rarely exceeded 42 pg/ml. This allows us to assume that it is the systemic pharmacological suppression of central regulation in OA that may be one of the links in the pathogenesis of immunosuppression through the "brain-inflammation-immunity" mechanism. Side effects in the postoperative period are an area that is rarely looked at with an immunological flashlight. Doctors tend to treat nausea, chills or mild agitation as something expected, "natural". But if you read more closely, this is not just discomfort. These are small signals that the body sends from the depths of its physiological architecture, showing that the balance is still disturbed. In our analysis, it turned out that patients who did not experience any of these reactions had a consistently favorable immune profile. CD4+ - 38-39%, NK cells - above 14%, IL-6 did not exceed 29 pg/ml, and Treg remained within the normal adaptive fluctuations (about 5%). And in these cases (regardless of the type of anesthesia), the system looked balanced. Perhaps this is how a patient should look after surgery in oncological patients, that is, physically vulnerable, but immunologically collected.

Those who had side effects but did not require intervention, such as a single episode of vomiting, chills, or a mild confusion episode, demonstrated a more mobile immune configuration. In patients with general anesthesia, CD4+ dropped to 33%, NK to 12%, IL-6 exceeded 40, and Treg increased significantly. Although these values remained within acceptable limits, the trend itself is quite clear: even against the background of moderate neurovegetative irritation, immune restructuring is activated. But truly striking changes began when side effects became pronounced: not just discomfort, but episodes that required drug correction. Repeated vomiting, agitation upon awakening, chills with tremors and tachycardia. Here, especially in the general anesthesia group, an immunological picture unfolded that can be called, without exaggeration, an "overload reaction": CD4+ dropped below 29%, NK - almost to 8%, IL-6 increased to 53 pg/ml, and Treg - above 7.7%. This is no longer just adaptation, this is a breakdown of balance, a transition from regulation to inhibition. In some cases, a correlation was also observed with a more severe awakening, with a delay in orientation and maladaptation phenomena. Regional anesthesia and the combined approach again showed greater stability. Even with pronounced side effects, the CD4+ and NK values did not fall critically, IL-6 remained within moderately elevated limits (up to 40 pg/ml), and Treg remained below the dangerous threshold. Perhaps this is not only due to pharmacology, but also to the fact that these groups more often used regional components that block the transmission of pain and stress impulses from the bottom up, preventing them from "reaching" the central immune axis.

Among patients who did not require intensive care or were under short-term monitoring (up to 6 hours), the immunological picture was stable. These are the cases where the anesthetic approach was maximally gentle, surgery was predictable, and the patient was functionally preserved. Regardless of the type of anesthesia, their CD4+ level remained at 38–39%, NK cells were above 14%, IL-6 did not rise above 30 pg/ml, and Treg remained in the physiological zone (up to 5%). This is, perhaps, the immune status to which we want to return after any operation. When the patient remained in the ICU longer (up to 24 hours, even without obvious complications), the first alarming signs appeared in the immune profile. This was especially evident in the general anesthesia subgroup: CD4+ decreased to 34%, NK cells to 12%, IL-6 reached 40 pg/ml, and Treg began to rise. These data were not always accompanied by clinical complaints. But, as often happens, the immune system "knows earlier." It reacts not so much to symptoms as to the internal state - to the fact that the body spends energy on recovery, and not always with a reserve. But in patients who were in intensive care for more than a day or required correction of hemodynamics, breathing, level of consciousness, their immune system did not just adapt, but began to lose stability. In the OA group, this was especially evident: CD4+ decreased below 29%, NK - below 9%, IL-6 - above 54 pg/ml, and Treg rose to 7.9%. In these cases, we actually saw a combination of all the signs of systemic immunosuppression: suppression of the key coordinating link (CD4+), reduction of the innate response (NK), hyperproduction of proinflammatory IL-6 and simultaneous inhibition via Treg. It was as if the body was simultaneously turning on the gas and brake pedals, and in this chaos of immune control it began to lose efficiency.

In the RA and OA+RA subgroups, the trends were similar, but the scale of changes was much more restrained. Even in patients who underwent long-term observation in the ICU, CD4+ counts did not decrease to critical levels, NK cells remained ≥11%, and IL-6 did not exceed 42 pg/ml. Perhaps, the regional components of anesthesia acted as stabilizers here: by reducing neurovegetative and stress-induced activation, they did not allow the immune system to go into destructive mode. Patients whose recovery began already on the first day (they got up, ate on their own, went to the toilet) in the overwhelming majority demonstrated a balanced immune profile. Regardless of the type of anesthesia, CD4+ levels remained at 38-

39%, NK cells were within normal limits (14-15%), IL-6 was no higher than 30 pg/ml, and Treg was about 5%. These are the patients for whom the surgical trauma was perceived by the body not as a catastrophe, but as a challenge that could be responded to without a sharp redistribution of resources.

But in those whose recovery lasted for two days or more, even if there were no complications formally, shifts began to appear. In the general anesthesia subgroup, CD4+ decreased to 34%, NK - to 12%, IL-6 rose above 40, and Treg steadily increased. This is no longer a physiological norm, but immunological fatigue. Perhaps, not only the parameters of anesthesia play a role here, but also the nature of pain, microcirculatory changes, and general "overheating" of the inflammatory system. Nevertheless, in the RA and OA+RA subgroups, the dynamics were more restrained, despite the same degree of functional delay. The most indicative group of patients was the one whose recovery lagged: getting up occurred later than 48 hours, patients remained dependent on the staff in elementary everyday functions, and their activity decreased. In these people, especially under general anesthesia, the immune system literally "failed": CD4+ dropped below 29%, NK - to 8.7%, IL-6 exceeded 53 pg/ml, Treg rose to almost 8%. Here we are no longer talking about a decrease in tone or a simple "delayed recovery". It is important that even in this severe clinical subgroup, patients who received regional or combined anesthesia had a gentler immune profile: NK cells remained at ≥11%, Treg did not exceed 5.6, and IL-6 did not rise above 40, which again confirms the pathogenetic hypothesis that the choice of anesthesia is not only a means of anesthesia, but also an instrument of immunological protection of the patient.

Conclusion

1. As a result of a comprehensive analysis of clinical and immunological relationships in cancer patients who underwent surgery using various types of anesthesia, a systemic interdependence was established between the nature of the perioperative immune response, the type of anesthesia and the likelihood of developing an immunosuppressive state. The data obtained make it possible to build a substantiated pathogenetic model in which the anesthetic effect acts not as a neutral component of pain relief, but as an active modifier of the immune balance in oncological disease conditions.
2. The type of anesthesia has a systemic effect on the immune status of cancer patients in the perioperative period. The data obtained not only confirm the existence of immunosuppression as a clinically significant phenomenon, but also make it possible to form a pathogenetic model explaining the mechanisms of its formation. The established immunological markers (decreased CD4+, NK cell activity, increased Treg and IL-6) have potential prognostic value.

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