ИММУНОЛОГИЧЕСКИЕ МАРКЕРЫ ПРИ ОСЛОЖНЕНИЯХ ЭНДОПРОТЕЗИРОВАНИЯ СУСТАВОВ

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Резюме. Перипротезная инфекция суставов до сих пор остается сложной клинической проблемой, поскольку точное определение этого состояния и надежные лабораторные маркеры пока отсутствуют. Данное исследование было направлено на оценку информативности определения некоторых субпопуляций лимфоцитов и моноцитов у пациентов с перипротезной инфекцией суставов и неинфекционными осложнениями эндопротезирования. В данное исследование было включено 34 пациента с хронической перипротезной инфекцией, 12 – с неинфекционными осложнениями и 30 практически здоровых лиц. Количество $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD19^+$, $CD3^-CD16^+CD56^+$, $CD3^+HLA\text{-}DR^+$, $CD4^+CD45RA^-CD45RO^+$, $CD4^+CD45RA^+CD45RO^-$ и $CD14^+HLA\text{-}DR^+$ субпопуляций лимфоцитов и моноцитов в периферической крови определяли методом проточной цитометрии. Оценку экспрессии мембранных антигенов проводили по средней интенсивности флуоресценции. У пациентов с перипротезной инфекцией суставов было выявлено достоверное увеличение субпопуляций $CD3^+CD4^+$ ($p < 0,01$) и достоверное снижение субпопуляций $CD3^-CD16^+CD56^+$ ($p < 0,005$) при сравнению с контрольной группой. Содержание $CD19^+$ лимфоцитов у этих больных было достоверно выше, чем у лиц с неинфекционными осложнениями ($p < 0,005$), последняя группа также характеризовалась более высоким содержанием активированных Т-лимфоцитов ($CD3^+HLA\text{-}DR^+$) по сравнению с контрольной ($p < 0,001$). Количество «наивных» Т-лимфоцитов ($CD4^+CD45RA^+CD45RO^-$) было ниже у больных с перипротезной инфекцией суставов, чем у больных с неинфекционными осложнениями ($p < 0,05$), и в обеих группах этот показатель был достоверно ниже, чем в контрольной ($p < 0,001$). Содержание Т-клеток памяти ($CD4^+CD45RA^-CD45RO^+$), напротив, было достоверно повышено в обеих сравниваемых группах ($p < 0,05$). В группе больных с перипротезной инфекцией суставов количество активированных моноцитов ($CD14^+HLA\text{-}DR^+$), а также показатель экспрессии данного активационного маркера были существенно ниже, чем в двух остальных группах ($p < 0,05$ и $p < 0,001$ соответственно). Таким образом, оценку субпопуляций лимфоцитов и моноцитов периферической крови, в том числе изучение интенсивности экспрессии активационных маркеров, можно, вместе с другими общепринятыми клинико-лабораторными показателями, дополнительно использовать для проведения дифференциального диагноза между перипротезной инфекцией суставов и неинфекционными осложнениями эндопротезирования.

Ключевые слова: эндопротезирование суставов, осложнения, перипротезная инфекция, проточная цитометрия, лимфоциты, моноцит

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IMMUNOLOGICAL MARKERS OF ARTHROPLASTY FAILURE

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Abstract. Periprosthetic joint infection still remains a clinical challenge since accurate definition of this condition and reliable laboratory markers have not been established yet. This study aimed to evaluate the benefit of some lymphocyte and monocyte subset determination in patients with periprosthetic joint infection and non-infectious arthroplasty failure. Thirty-four patients with chronic periprosthetic joint infection, 12 patients with non-infectious arthroplasty and 30 healthy persons were included in the study. The counts of $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD19^+$, $CD3^-CD16^+CD56^+$, $CD3^+$HLA-DR^+, $CD4^+CD45RA^-CD45RO^+$, $CD4^+CD45RA^+$ $CD45RO^-$ and $CD14^+$ HLA-DR^+ subsets in peripheral blood were assessed by flow cytometry. The assessment of the intensity of antigen expression was carried out according to mean fluorescence intensity. A significant increase in $CD3^+CD4^+$ subsets ($p < 0,01$) and a significant decrease in CD3-$CD16^+CD56^+$ subsets ($p < 0,005$) were revealed in patients with periprosthetic joint infection compared to the healthy controls. The content of $CD19^+$ lymphocytes in these patients was significantly higher than in aseptic ones ($p < 0,005$); the latter group was also characterized by more pronounced increase in the number of activated T lymphocytes ($CD3^+$HLA-DR^+) compared to controls ($p < 0,001$). Patients with periprosthetic joint infection showed decreased "na ve" T lymphocytes ($CD4^+CD45RA^+CD45RO^-$) count compared to aseptic ones ($p < 0,05$), and both groups showed a decrease counts compared to controls ($p < 0,001$). On the contrary, memory T lymphocyte ($CD4^+CD45RA^-CD45RO^+$) count was significantly increased in both compared groups ($p < 0,05$). Patients with periprosthetic joint infection compared with other two groups demonstrated a significant decrease in the number of activated monocytes ($CD14^+$HLA-DR^+) and pronounced decrease in the expression intensity of this marker on cell membrane ($p < 0,05$ and $p < 0,001$, respectively). Thus, evaluation of lymphocyte and monocyte subsets, including expression of cell activation antigens could be useful as additional laboratory test in combination with other conventional methods for differentiation between periprosthetic joint infection and aseptic arthroplasty failure.

Keywords: joint arthroplasty, complications, periprosthetic joint infection, flow cytometry, lymphocytes, monocytes.

Introduction

Arthroplasty failure is a serios complication of joint replacement surgery and may be caused by periprosthetic joint infection (PJI) or non-infectious factors. This condition often requires revision surgery and implant replacement. PJI occurs in 1 to 3% of patients after total joint arthroplasty and accounts for 20% to 50% cases of implant failures [6, 9, 12]. A combination of clinical signs, intraoperative findings and pre- and intraoperative laboratory tests (peripheral blood counts, serum inflammatory markers, synovial fluid examination, microbiological culture, tissue histology) is used for PJI diagnosis [8].

Non-infectious arthroplasty failure (NIAF) includes aseptic inflammation, implant instability, periprosthetic fracture, osteolysis/adverse tissue reaction and other reasons and occurs in 50 to 80% of arthroplasty failures [6, 9, 12]. As with arthroplasty failure due to PJI, surgical intervention is usually need to treat NIAF. Though mechanical-related failures are typically diagnosed by X-ray, there are no perfect assays for non-mechanical failures that often difficult to differentiate from PJI due to inflammatory responses at affected areas [4].

The actual incidence of PJI may be significantly higher, since a significant proportion of these cases in patients with instability endoprosthesis or isolated pain syndrome has so far been erroneously regarded as aseptic cases. In routine practice, physicians face challenges in diagnosis of PJI and its differentiation from NIAF. Biofilms, low-grade infection or culture-negative microorganisms have been reported to significantly reduce the sensitivity and specificity of laboratory tests [5, 7, 13]. Underdiagnosing PJI is followed by inappropriate treatment with severe consequences.

Recently, several new serum and synovial fluid biomarkers (α-definsine, calprotectin, interleukin-1, interleukin-6, interleukin-17, leukocyte esterase, lipocalin, procalcitonin) were proposed to confirm PJI [2, 3, 5, 7]. Despite promising data, many authors note, that underlying immune disorders or other inflammatory diseases, as well as co-morbidities, may affect test results [1, 4, 10, 11]. The purpose of the study was to evaluate the benefit of some lymphocyte and monocyte subsets determination as well as expression of cell activation antigens in patients with PJI and NIAF.

Materials and methods

Forty-six patients after total large joint replacement were included in the study. According to

International Consensus Criteria on PJI (2018) after revision arthroplasties 34 patients were classified as chronic PJI (19 males, 15 females, mean age 51±8 years) and 12 patients as NIAF (4 males, 8 females, mean age 47±6 years), namely implant instability or aseptic inflammation. Complications developed 4,4±2,6 years after the main operation. Thirty healthy persons (12 males, 18 females, mean age 43±11 years) were recruited in control group. All patients signed informed consent forms prior to being enrolled.

Standard laboratory evaluation was performed for all patients: peripheral blood cell count, erythrocyte sedimentation rate, C-reactive protein. Synovial fluid and periprosthetic tissue samples obtained intraoperatively were sent for microbiological and histological examination. If there were any signs of infection, a two-stage revision with the installation of a cement spacer impregnated with antibiotics or resection arthroplasty were performed. The counts of $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD19^+$, $CD3^-CD16^+CD56^+$, $CD3^+$HLA-DR^+, $CD4^+CD45RA^-CD45RO^+$, $CD4^+CD45RA^+$ $CD45RO^-$ and $CD14^+$HLA-DR^+ subsets in peripheral blood were assessed by flow cytometry (FACSCalibur, Becton Diskinson, USA). The assessment of the intensity of antigen expression was carried out according to median fluorescence intensity (MFI).

Statistical analysis was performed in Statistica 10.0 Software for Windows. Normally distributed continuous data were shown as mean ± standard deviation (SD) and compared using Student's t-test. A p value < 0.05 was considered statistically significant.

Results and discussion

As shown in Table 1, a significant increase in $CD3^+CD4^+$ subsets ($p < 0.01$) and a significant decrease in $CD3^-CD16^+CD56^+$ subsets ($p < 0,005$) were revealed in patients with PJI compared to the controls. The content of $CD19^+$ lymphocytes in patients with chronic PJI was significantly higher than in aseptic ones ($p < 0.005$); the latter group was also characterized by more pronounced increase in the number of activated T lymphocytes ($CD3^+$HLA-DR^+) ($p < 0.001$). Patients with PJR showed decreased "naïve" T lymphocytes ($CD4^+CD45RA^+CD45RO^-$) count compared to aseptic ones ($p < 0.05$), and both groups showed a decrease counts compared to controls ($p < 0.001$). On the contrary, memory T lymphocyte ($CD4^+CD45RA^-CD45RO^+$) count was significantly increased in both compared groups ($p < 0.05$).

Quite often, a violation of the functional activity of monocytes is detected in critical conditions (sepsis and other serios infections). Monocytes in healthy persons express molecules of HLA-DR with high density and easy determined by flow cytometry. Patients with PJI compared with patients with NIAF and controls showed not only a significant decrease in the number of monocytes ($CD14^+$) expressing HLA-DR antigen

TABLE 1. LYMPHOCYTE AND MONOCYTE SUBSETS AND EXPRESSION OF CELL ACTIVATION ANTIGENS IN PATIENTS WITH PERIPROSTHETIC JOINT INFECTION AND NON-INFECTIOUS ARTHROPLASTY FAILURE

Rate	PJI (n = 34)	NIAF (n = 12)	Controls (n = 30)	p
$CD3^+$, %	76.5±1.3	69.4±4.3	73.9±1.5	
$CD3^+$, abs	1760±45	1688±112	1038±47	
$CD3^+CD4^+$, %	51.8±1.8	48.0±3.4	45.9±1.4	*< 0.01
$CD3^+CD4^+$, abs	903±32	810±57	644±58	*< 0.01
$CD3^+CD8^+$, %	25.3±2.8	24.4±3.9	30.7±3.6	
$CD3^+CD8^+$, abs	445±26	361±49	425±9	
$CD19^+$, %	13.6±3.2	6.8±1.3	10.2±0.7	**< 0.005
$CD19^+$, abs	466±110	248±32	143±17	**< 0.005
$CD3^-CD16/56^+$, %	9.1±1.6	16.8±4.3	15.4±1.2	*< 0.005
$CD3^-CD16/56^+$, abs	289±53	409±21	456±19	*< 0.005
$CD4^+/CD8^+$	2.0±0.8	2.2±0.9	1.5±0.7	
$CD3^+$HLA-DR^+, %	8.9±2.3	11.8±1.2	6.5±0.4	*< 0.001
$CD4^+/45RO^+45RA^-$, %	40.4±6.1	44.7±4.4	14.6±9.2	*p < 0.001
$CD4^+/45RA^+45RO^-$, %	6.6±4.5	12.8±1.8	30.1±8.9	*p < 0.05. **p < 0.001
$CD14^+$HLA-DR^+, %	78.8±2.6	90.7±2.4	88.7±1.1	* **p < 0.05
MFI $CD14^+$ HLA-DR^+ (units)	57.0±2.9	186.7±15.4	184.6±9.9	* **p < 0.001

Note. *, statistically significant differences with parameters of the control group; **, statistically significant differences with parameters of the comparison groups.

($p < 0.05$), but also more pronounced decrease in the expression intensity of this marker according to the MFI parameter ($p < 0.001$).

Conclusion

As already mentioned above, many serum and synovial biomarkers may help differentiation of PJI and NIAF, but there remain cases that are clinically challenging to classify. The profile of different cell subpopulations during PJI and NIAF is still being investigated [1, 4]. The data obtained demonstrated a pronounced decrease in the number monocytes expressing the HLA-DR antigen, as well as a decrease in its density expression on the surface of monocytes and T lymphocytes may indicate low functional activity of these cells, especially antigen presentation and regulation of intercellular interactions. The present study showed that evaluation of lymphocyte and monocyte subset and expression of cell activation antigens could be useful, especially in combination with conventional methods, for diagnosing of PJR and differentiation between PJI and NIAF. New data concerning host immune reactions during arthroplasty failure may potentially identify cell subsets involved in inflammation related to surgical procedures or underlying inflammatory disorders. That may provide insights into future diagnostic and possibly treatment opportunities. The search for the most diagnostically accurate combinations of clinical and laboratory criteria should be continued.

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References

1. Abdelbary H., Cheng W., Ahmadzai N., Carli A.V., Shea B.J., Hutton, B., Fergusson D.A., Beaule P.E. Combination tests in the diagnosis of chronic periprosthetic joint infection: systematic review and development of a stepwise clinical decision-making tool. *J. Bone Joint Surg. Am., 2020, Vol. 102, Suppl. 2, pp. 114-124.*
2. Alvand A., Rezapoor M., Parvizi J. The role of biomarkers for the diagnosis of implant-related infections in orthopaedics and trauma. *Adv. Exp. Med. Biol., 2017, Vol. 971, pp. 69-79.*
3. Chen A., Fei J., Deirmegian C. Diagnosis of periprosthetic infection: novel developments. *J. Knee Surg., 2014, Vol. 27, no. 4, pp. 259-265.*
4. Fisher C.R., Patel R. Profiling the immune response to periprosthetic joint infection and non-infectious arthroplasty failure. *Antibiotics (Basel), 2023, Vol. 12, no. 2, 296.* doi: 10.3390/antibiotics12020296.
5. Gollwitzer H., Dombrowski Y., Prodinger P.M., Peric M., Summer B., Hapfelmeier A., Saldamli B., Pankow F., von Eisenhart-Rothe R., Imhoff A.B., Schauber J., Thomas P., Burgkart R., Banke I.J. Antimicrobial peptides and proinflammatory cytokines in periprosthetic joint infection. *J. Bone Joint Surg. Am., 2013, Vol. 95, no. 7, pp. 644-651.*
6. Kenney C., Dick S., Lea J., Liu J., Ebraheim N.A. A systematic review of the causes of failure of revision total hip arthroplasty. *J. Orthop., 2019, Vol. 16, no. 5, pp. 393-395.*
7. Nodzo S.R., Bauer T., Pottinger P.S., Garrigues G.E., Bedair H., Deirmengian C.A., Segreti J., Blount K.J., Omar I.M., Parvizi J. Conventional diagnostic challenges in periprosthetic joint infection. *J. Am. Acad. Orthop. Surg., 2015, Vol. 23 (Suppl.), pp. S18-S25.*
8. Parvizi J., Tan T.L., Goswami K., Higuera C., Della Valle C., Chen A.F., Shohat N. The 2018 definition of periprosthetic hip and knee infection: an evidence-based and validated criteria. *J. Arthroplasty, 2018, Vol. 33, no. 5, pp. 1309-1314.*
9. Postler A., Lutzner C., Beyer F., Tille E., Lutzner J. Analysis of total knee arthroplasty revision causes. *BMC Musculoskelet. Disord., 2018, Vol. 19, no. 1, 55.* doi: 10.1186/s12891-018-1977-y.
10. Qin L., Du C., Yang J., Wang H., Su X., Wei L., Zhao C., Chen C., Chen H., Hu N., Huang W. Synovial fluid interleukin levels cannot distinguish between prosthetic joint infection and active rheumatoid arthritis after hip or knee arthroplasty. *Diagnostics, 2022, Vol. 12, no. 5, 1196.* doi: 10.3390/diagnostics 12051196.
11. Saleh A., George J., Faour M., Klika A.K., Higuera C.A. Serum biomarkers in periprosthetic joint infections. *Bone Joint Res., 2018, Vol. 7, no. 1, pp. 85-93.*
12. Schwartz A.M., Farley K.X., Guild G.N., Bradbury T.L.Jr. Projections and epidemiology of revision hip and knee arthroplasty in the United States to 2030. *J. Arthroplasty, 2020, Vol. 35, no. 6S, pp. S79-S85.*
13. Wasterlain A.S., Goswami K., Ghasemi S.A., Parvizi J.J. Diagnosis of periprosthetic infection: recent developments. *J. Bone Joint Surg. Am., 2020, Vol. 102, no. 15, pp. 1366-1375.*

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